Technological Change in the Pharmaceutical Industry in Japan and the United Kingdom

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Presented for the Degree of Doctor of Philosophy,
The University of Edinburgh,
2000

Declaration

I declare that this thesis has been composed by myself alone from the result of my own research and any work that is not my own has been clearly referenced.

Takuji Hara

Abstract

This thesis explores the process of technological change in the pharmaceutical industry. Although pharmaceuticals are crucial in modern society, the shaping process of this technology is not fully understood. In particular, the social aspect of the process is seldom examined. Despite the lack of close empirical studies, the process is often assumed to be a linear process from scientific research through technological and clinical development to market. This thesis demonstrates that this is not the case, through a comparative, multiple case study including sixteen cases of major drug innovation in Japan and the United Kingdom. The shaping process of pharmaceuticals is not linear but interactive and multilateral. Four aspects of the process are identified, namely the shaping of the compound, of the application, of organisational authorisation and of the market. In each aspect, various social groups, non-human entities, and historical, structural and cultural factors are differently involved. Different aspects of drug shaping also interact with each other. In addition, three types of drug innovation are identified, namely, paradigmatic innovation, application innovation and modification-based innovation. Each type of innovation has distinctive features. Historical, structural and cultural factors, which significantly affect the shaping process of drugs but are often invisible, are also considered through a comparison between Japanese and British drug innovations.

Acknowledgement

Without the help of many people, I would not have been completed this work. I wish to thank Donald MacKenzie and Graham Spinardi for their supervision and valuable suggestions and critical comments. I would also like to thank Graham and Donald for helping me correct English errors in my writing. I wish to thank Sang-Hyun Kim for providing me with valuable resources from his knowledge of science and technology studies.

I would like to thank the interviewees who talked to me about their stories of drug discovery and development. They are Sir James Black, Akira Endo, Sir David Jack, Barry Furr at AstraZeneca, John Wood and Angela Palmer at GlaxoWellcome, Mike Nakayama at GlaxoWellcome (Japan), Kazuyuki Nakagawa, Hideyuki Miwa and Shinya Tashiro at Otsuka Pharmaceutical, Masao Kuroda at Sankyo, Masahiko Fujino, Katsura Morita, Mitsuo Numata, Yasuaki Ogawa, Tai Matsuzawa, Kenji Okonogi, Nobuyoshi Hiramatsu and Kouji Sonoi at Takeda Chemical Industries, and Toichi Takenaka and Isao Yanagisawa at Yamanouchi. I would also like to thank Andrew Bliski for providing me with information about the discovery and development of atenolol. I also wish to thank two anonymous interviewees who talked to me about their laboratory life. My thanks also due to Christopher Henderson at AstraZeneca, Anita Kidgell at GlaxoWellcome, Masamichi Nishi at GlaxoWellcome (Japan), Shinji Masaki at Otsuka Pharmaceutical, Sakae Katayama at Sankyo and Toshihiko Murate and Kyoko Iida at Takeda Chemical Industries for their help with the arrangement of interviews. I am also indebted to Gail Turner at the Association of the British Pharmaceutical Industry and Takeshi Shinba at Japan Pharmaceutical Manufacturers Association for providing me with information about the British and Japanese pharmaceutical industry, and to Nobuo Aoyama, Soichi Arakawa, Satoshi Kagawa, Sadao Kamidono, Takeshi Tsujino at Kobe University School of Medicine for providing me with information about the treatment for the diseases for which the drugs discussed in this study are used.

I wish to thank Kobe University for supporting my life in Edinburgh financially. I also wish to thank the faculty members of the Graduate School of Business Administration, Kobe University, for allowing me to study abroad for such a long time. I wish to thank specially Masayuki Munakata for his intellectual and social support since my student years. I also wish to thank Gerri and Colin Kirkwood, Tom Schuller and Unni Hagen for helping my family live happily in Edinburgh. Special thanks are due to Gerri for helping me correct the English errors in my thesis. I would also like to thank my wife's and my parents, Yasuko and Sakuichi Morino, and Keiko and Yoshine Hara, for supporting my family on various occasions. I owe a special debt of thanks to my wife Akemi for supporting and encouraging me constantly. Thank you, Sotaro, Koshiro and Nozomi, for tolerating me being always "busy father."

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Chapter 1: Introduction

1. 1. Understanding Technological Change in the Pharmaceutical Industry

Technology is a crucial factor in modern society, which has an enormous influence on our lives. Our actions and relationships have always been transformed by technological change. On the other hand, technology is something people shape: it does not emerge without human beings. In particular, companies in the private sector nowadays play a major role in the creation of most technologies. Research and development (R&D) for innovation is now a key activity for many companies.

This study is an attempt to explore the process of technological change, particularly in the pharmaceutical industry. Pharmaceuticals are important products for our lives. Especially, they are indispensable for patients. They are often lifesaving. At the same time, they are potentially dangerous. Their wrong administration may cause death or handicap. Mainly because of this potential risk, modern governments strictly regulate every aspect of the industry: research, development, manufacturing, marketing and delivery. In addition, the pharmaceutical industry is the most research-intensive industry. R&D costs in the industry are more than 10 % of sales. (The Association of the British Pharmaceutical Industry 1997, p. 29; Japan Pharmaceutical Manufacturers Association 1997, p. I-35) Modern pharmaceutical products are on the cutting edge of biomedical sciences, though it should be noticed that it takes about 10 years from their discovery to appearance on the market. Thus, pharmaceuticals can be regarded as one of the most crucial technologies in modern time.

Despite this, people other than experts understand the shaping process of drugs poorly. This is probably partly because people regard pharmaceuticals as very difficult to understand. The molecular structure of a drug is invisible. Even though it is described as a chemical formula, it is still hard for lay people to imagine what it is actually like. The names of chemicals are also very unfamiliar to outsiders. In addition, because drugs work in the living body, knowledge not only of chemistry but also of

biology is needed to understand their mechanism of action. Another possible reason for the lack of knowledge about the shaping process of drugs is the high confidentiality of pharmaceutical companies. Because they are fiercely competing with each other on the cutting edge, they are unwilling to make the details of their research and technological activities public. An anonymous interviewee working for a pharmaceutical company stated that they also fear that the disclosure of internal information can lead to sensationalist discussion about their drugs. Thus, in spite of being crucial in modern society, the innovation process in the pharmaceutical industry remains relatively unexplored. This research is an attempt to fill in the gap between the demand and the supply of knowledge in this area.

Innovation in the pharmaceutical industry is interesting from the viewpoint of social studies of technology because it is sometimes regarded as following the linear model even by those who doubt the model's general applicability. The linear model of technological change suggests that technological change starts from scientific research, goes through technological development and production, and ends with consumption. An alternative version of the linear model implies that technological change starts from social needs, followed by research and development, production and marketing, and ends with the satisfaction of the initial needs. Nowadays, these linear views of technological change are in general regarded as too simple to represent the actual process of technological change. However, the pharmaceutical industry is sometimes seen as an exception. Indeed, the process of innovation in the industry appears to be linear, because the government strictly regulates the formal process of research and development of drugs. Nevertheless, there remains a doubt because the formal and the actual aspects of social phenomena are often different. Without sufficiently detailed empirical studies, how can we say that the innovation process of pharmaceuticals is linear?

The shaping process of pharmaceuticals is also interesting from a sociological point of view, because various social groups seem to be involved in the process. As a result, pharmaceuticals have several different meanings. Roughly speaking, there are at least

five meanings within a drug. Firstly, for researchers, they are chemicals. Secondly, for patients and doctors, they are therapies. Thirdly, for companies, they are products for sale. Fourthly, for regulators, they are objects of their regulation. Fifthly, for some industrial workers, they may be the means of intra-organisational politics. If we divide relevant people into smaller social groups, there are probably even more meanings. For example, chemists and biologists probably attribute different meanings to the same chemical. Patients and doctors probably regard the same medicine as having different therapeutic value. The production and marketing divisions of the same pharmaceutical company probably see the same product from different points of view. Thus, different social actors with different interests seem to be involved in the shaping process of drugs. How do they interact with each other?

Non-human entities can also be seen to have a role in the shaping process of drugs. There is a large body of literature discussing the relationship between people and artefacts in the sociology and philosophy of science and technology. (Collins and Yearley 1992; Callon and Latour 1992; Latour 1992 [1999]; Bloor 1999; Latour 1999) Although the metaphysical controversy is beyond the scope of this study, it is also interesting for us to look at the roles various non-human entities play in the innovation process of pharmaceuticals. What kinds of non-human entity are involved and how do they interact with human actors?

In addition, historical, structural and cultural factors cannot be ignored in the process of drug shaping. There are the social relationships which are beyond the interactions between the "relevant" human and non-human actors. Such relationships, however, constitute the background against which actors play their part. They have an influence on the positions and activities of actors. Without taking them into consideration, we cannot sufficiently understand the shaping process of pharmaceuticals. Thus, it is interesting as well to investigate the influences of these factors. What kinds of historical, structural and cultural factors affect the process and how do they do so?

This study has the following purposes: to fill the gap between necessity and reality of

outsiders' knowledge of technological change in pharmaceuticals; to provide a close description of drug innovation process; to understand how various social groups with different interests interact with each other in the shaping process of drugs; to know what kinds of non-human entities are related to the innovation process of medicines: and to learn how historical, structural and cultural factors influence the process of technological change in the pharmaceutical industry.

1.2. Two Significant Features of This Study

In order to accomplish the purposes mentioned above, this study attempts a close examination of a number of historical cases of innovation in the pharmaceutical industry in Japan and the United Kingdom. It possesses two uncommon features compared with most other innovation studies. First, I venture into the contents of relevant academic literature in medicine, physiology and pharmacology. This is potentially risky because I have limited basic knowledge about them. However, academic literature has a lot of historical evidence and information to help us understand the process of drug innovation. To minimise the misunderstanding, I conducted interviews with key researchers and corporate staff who were involved in the discovery and development of the drugs. I also consulted other sorts of literature such as review articles, textbooks, biography, and corporate history. I emphasise again that I used the contents of academic literature only as evidence for a sociological and historical study of drug innovation, and that I have no intention of discussing the contents themselves.

The second unique feature of this study is that I also explore the organisational processes *inside* pharmaceutical companies. This was achieved by interviewing relevant people and consulting some internal documents which were obtained by courtesy of these people or their companies. As mentioned above, pharmaceutical companies are especially sensitive about confidentiality. However, probably because of their awareness of the importance of public relations and because most of the cases I examined were not on the cutting edge of research any longer, they were generally

cooperative. All the researchers I met seemed proud of their achievements in drug discovery and happy to talk about them to me. There is again potential risk as regards the accuracy of their stories. To reduce this risk, I also consulted academic papers, patents, and other sources of information. This study demonstrates that a company is not a monolithic unit but that there are a lot of conflicts and politics within it.

1.3. The Structure of This Thesis

This thesis consists of eight chapters. Chapter 2 reviews various perspectives on technological change, in particular, the linear model and several sociological strands of non-linear perspective on technological change. The chapter also describes some basic features of R&D activities in the pharmaceutical industry. In addition, it reviews the literature on drug R&D. At the end of the chapter, the objectives, methods and areas of this study are set out.

In each chapter from Chapter 3 to Chapter 6, several cases of drug innovation in the same therapeutic area are described. Each chapter includes at least one British and one Japanese case. Chapter 3 deals with cardiovascular drugs, especially the ones that are used for the treatment of hypertension. The innovation processes of two β-blockers, namely propranolol and atenolol, and of one Ca-antagonist, nicardipine, are examined. Chapter 4 addresses the cases of anti-asthma drugs including β-stimulants such as salbutamol, salmeterol and procaterol, and inhaled steroids such as beclomethasone dipropionate inhaler and fluticasone propionate. Chapter 5 describes the cases of drugs called histamine H_2-antagonists, used for the treatment of peptic ulcer. They include cimetidine, ranitidine and famotidine. Chapter 6 depicts the R&D process of two LHRH analogues, leuprorelin and goserelin, which are used in the treatment of prostate and breast cancer and several gynaecological diseases.

Chapter 7 explores three more cases of pharmaceutical innovation which took place in Japan. These cases include an HMG-CoA reductase inhibitor, mevastatin, which reduces the level of cholesterol in the blood, an α_{1c}-receptor antagonist, tamsulosin,

which is used for the treatment of urination disorder accompanying benign prostatic hypertrophy, and an cephalosporin antibiotic, cefotiam. Each case in this chapter has distinguishable characteristics from the others. Mevastatin is the exemplary compound of other HMG-CoA reductase inhibitors such as lovastatin, simvastatin, and pravastatin, which are at present the top selling drugs in the world. It was paradigmatic as a compound and as a therapy. Tamsulosin was not very novel as a compound. There had been some α-receptor antagonists when the drug was discovered. However, its application was innovative. It was used for the treatment of urination disorder whereas existing α-receptor antagonists had been used for the treatment of hypertension. Although cefotiam had some unique structure in its molecule, it was not a paradigmatic drug in the same sense as mevastatin. It had exemplary compounds and its application was the same as the exemplars. These cases in the chapter are intentionally varied in order to confirm the findings of previous chapters, especially those about types of innovation. In addition, they particularly go into the details of the organisational process to identify properties of each type of innovation.

Chapter 8 concludes this study by integrating the findings of previous chapters. First, general features of the shaping process of pharmaceuticals are described. The complex interaction between various actors, factors and activities in the process are revealed. Second, three different types of innovation in the pharmaceutical industry, namely paradigmatic innovation, application innovation and modification-based innovation, are proposed. The chapter explores several distinguishable characteristics of each type of innovation. Third, distinctive features of Japanese pharmaceutical innovation are discussed. Several historical, structural and cultural factors affecting the innovation process are considered. Finally, this study ends by summarising its several implications for innovation studies and for innovation management in the pharmaceutical industry.

Chapter 2: Technological Change and the Pharmaceutical Industry

2.1. Perspectives on Technological Change

2.1.1. Linear Model of Technological Change and Its Criticism

Among various perspectives on technological change, there is a simple dichotomy between two extreme positions. One of these is "hard" technological determinism, which regards scientific progress and its natural consequence, technological change, as autonomous phenomena and as the ultimate factors that decide the style of society. (Marx and Smith 1994, pp. ix-xii) Another simple perspective is the exact opposite of "hard" technological determinism – what I will call "hard" social determinism. "Hard" social determinism views society as the absolute planner of scientific and technological change. (Williams and Edge 1996, 866) We can find several sub-versions of this perspective, including "demand-pull" theory of innovation (Coombs, Saviotti and Walsh 1987, pp. 94-97), "mode of production" determinism and organisational choice perspective (Thomas 1994, pp.1-9). Either the "hard" version of technological determinism or that of social determinism can be put as a linear model. (Figure 2.1)

Figure 2.1: "Hard" Technological Determinism and Social Determinism

Scientific Research	→	Technological Development	→	Product Development	→	Production	→	Marketing and Sales	→	Social Impacts

"Hard" Technological Determinist Linear Model

Social Needs	→	Scientific Research	→	Technological Development	→	Product Development	→	Production	→	Marketing and Sales

"Hard" Social Determinist Linear Model

However, few researchers in social sciences nowadays seem to believe in either version of the linear model. Most believe that there are both aspects in the process of technological change. These include, for example, economists of technological change (Nelson and Winter 1977; Dosi 1982; Coombs, Saviotti and Walsh 1987, pp.102-103; Rothwell 1994; Steinmueller 1994; Nelson 1996; McKelvey 1996; Freeman and Soete 1997), historians of technological change (Rosenberg 1976; Rosenberg 1982; Hughes 1983; David 1985; Rosenberg 1994) and researchers on technology management (Abernathy 1978; Kline 1985; Tushman and Anderson 1986; Henderson and Clark 1990; Tushman and Rosenkopf 1992; Utterback 1994; Thomas 1994; Christensen 1997)

Sociologists of science and technology[1] also deny the linear model of technological change, especially its technological determinist version. In the next section, we examine several variations of opposition to the technological determinist linear model, because their criticism is both detailed and theory-oriented, which helps us understand how the linear model is distant from the reality of technological change.

2.1.2. Interpretative Flexibility and Closure: the Social Construction of Technology

The first variation of sociological criticism against the linear model of technological change is done by the social construction of technology approach (SCOT). SCOT, like most of the other strands of sociology of technology, stems from the sociology of scientific knowledge, especially the empirical programme of relativism (EPOR) developed by Harry Collins. (Pinch and Bijker 1987; Collins 1981) Pinch and Bijker, the leading proponents of SCOT, regard the process of technological change as an evolutionary process, that is to say, an alternation of variation and selection. As a result, they advocate a "multidirectional" model of technological change and deny the linear model. (Pinch and Bijker 1987, p.28)

[1] For an overview of the sociology of (science and) technology, see, for example, Bijker, Hughes and Pinch (eds.) (1987), Webster (1991), William and Edge (1996) and MacKenzie and Wajcman (eds.) (1999).

The essential concepts of SCOT are "relevant social groups", "interpretative flexibility" and "closure mechanisms." A relevant social group is the social group in which all members share a meaning of a certain artefact. Different relevant social groups often give different meanings to the same artefact. For example, in the history of bicycle development, the high-wheeler had the meaning of the "macho machine" for young men of means and nerve, but for older people and women it had the meaning of the "unsafe machine." This divergence of meanings is named interpretative flexibility. A relevant social group gives a specific meaning to an artefact and perceives a set of specific problems with respect to the artefact. Around each problem, several different solutions can be developed. As a result, a number of variants of the artefact are developed. This is the explanation of variation of an artefact by SCOT. (Pinch and Bijker 1987, pp.30-44; Pinch 1996, pp.24-25)

However, variation based on interpretative flexibility does not continue forever. Some artefacts appear to have fewer problems than others and become increasingly dominant forms of the technology. This closure and stabilisation of technology occur through closure mechanisms. It is not necessary that all relevant social groups be convinced of a certain interpretation of the artefact: what is required is that each major group can see its own problem as being solved. Pinch and Bijker suggest two types of closure mechanisms of technological change. One is what Pinch and Bijker call rhetorical closure, which we can typically observe in advertisements. With rhetoric, advertisements try to convince people belonging to various relevant social groups that a particular design is superior to others. The other is what is called the redefinition of problems. For example, the low-wheeled bicycle with air tyres was regarded as the "safer bicycle" by some people including the designer and women cyclists. But other people such as racers and male cyclists regarded it as the "high-speed machine." Although the interpretations were different, the design solved different problems of different relevant social groups and became dominant. The closure and stabilisation of technology, however, may not mean the disappearance of all rivals, and a few different technologies may coexist. In addition, it does not mean that the technology reaches its final form. New problems can emerge and lead the

technology to another session of interpretative flexibility. (Pinch and Bijker 1987, pp.44-46; Bijker 1995, pp.84-88; Pinch 1996, p.25)

The SCOT perspective indicates that social diversity prohibits technological change from being developed in such a way as the technological determinist linear model assumes. At the same time, it also indicates that various social processes, called closure mechanisms, lead technological change in a specific direction, though the driving forces of closure mechanism are not necessarily clear. However, SCOT provides us with an alternative perspective, which seems to be much richer in content and closer to the reality of technological change than the technological determinist linear model.

2.1.3. Non-Human Actors: Actor-Network Theory

Although SCOT is a very strong opponent of the technological determinist linear model, it does not seem to be a strong opponent of the social determinist linear model to the same degree. However, it is obvious that technological change is by no means free from the laws of nature. Although most scholars probably recognise this, it is actor-network theory (ANT) that most strongly emphasises the role of non-human elements of nature in the process of technological change. According to ANT, technology should be seen as a product shaped by an actor-network in which not only human actors but also non-human actors such as electrons, catalysts, electrolytes, and lead accumulators are playing their roles. (Callon 1986, p.22, pp.28-33; Latour 1987, pp.121-144; Law 1987) An actor-network is also a dynamic network, which can connect up further heterogeneous elements, redefine itself, and transform itself constantly. (Callon 1986, pp.28-33; Callon 1987, p.93) The activity that builds a relatively stable system (or network) within an indifferent and unstable environment (or field) from various human and non-human actors is named "heterogeneous engineering" (Law 1987, pp.113-116) or "translation." (Callon 1986, pp.24-28) In heterogeneous engineering, or in actor networking, society is not given a higher position than nature. (Law 1987, p. 130; Latour 1992 [1999]) There has been a controversy over this symmetrical position on human and non-human actors.

(Collins and Yearley 1992; Callon and Latour 1992; Latour 1992 [1999]; Bloor 1999; Latour 1999a) In addition, recent discussion amongst ANT proponents is developing beyond these issues. (Law 1999; Latour 1999b) However, what is important here is that the view of ANT is incompatible with the social determinist linear model. Rather, their perspective on technological change is more reciprocal and simultaneous: society, technological artefacts and knowledge of nature are co-evolving. (Callon 1986, p.20)

Thus, ANT provides us with another alternative perspective on technological change: a co-evolutionary model between society and science and technology. In contrast with the perspective of SCOT, it rejects not only the technological determinist linear model but also the social determinist linear model. At the same time, this view also reminds us of the active side of technological change through the notions of heterogeneous engineering and translation.

2.1.4. Structural and Historical Context: the Social Shaping of Technology

Both SCOT and ANT help us understand the complexity of technological change, but some social scientists have criticized them for their tendency to disregard the structural and historical context. For example, Russell and Williams (1988, 7-10, 26) point out that actors must be shaped not only by a tangible relationship to other actors, but also by an intangible historical and structural context. They argue that the historical and structural context is important in technology studies because there are several differences between science and technology. First, technological practitioners are more heterogeneous than scientists because they often work beyond the boundaries of the disciplinary community. Second, technological knowledge is more directly concerned with economic and political purposes than science. Third, technology consists of not only knowledge but also material: in technology studies, it is necessary to investigate the implementation and the use of technology.[2] These

[2] It should be noted that science is also based on not only knowledge but also material. See, for example, Collins (1992), Latour and Woolgar (1986) and Pickering (ed.) (1992). I think that this difference is a matter of degree.

differences force technology studies to embrace various institutional, structural and historical matters more than science studies. (Russell and Williams 1988, 4-6)

This (re-) attention to structural and historical context as well as to interacting actors in technological change is the key characteristic of an approach called the social shaping of technology (SST). (MacKenzie and Wajcman 1985, p.23; MacKenzie 1988; Williams and Edge 1996; MacKenzie and Wajcman 1999, p.22) Structural and historical context concretely includes, as we know from the literature of SST, classes, modes of production, markets, gender, democracy and so on. By taking these into consideration, SST can enjoy various intellectual fruits from existing social studies on technological change including Marxist technology studies (E.g. Braverman 1974; Noble 1984), the economics of technological change (see Section 2.1.1), studies of innovation management (see Section 2.1.1), feminist technology studies (see Wajcman 1995) and critical studies of technology policy (William and Edge 1996, 870-871).

It is important to note that SST is not the "hard" social determinism of technology. The proponents of SST explicitly recognize the following two things. First, social actors cannot construct technology at will because nature also limits technology. (MacKenzie and Wajcman 1999, pp.16-18) Second, technology, as an element of the structural and historical context, restricts the behaviour of social actors. (Williams and Edge 1996, 866-867; MacKenzie and Wajcman 1999, pp.22-23) They are not arguing that society determines technology, but that it is important for us to understand the myriad ways in which society shapes technology (MacKenzie and Wajcman 1985, p.24). They stress the room for technological and social choices, the negotiability of technology, the temporary stability of technology and the reversibility of earlier choices. (Williams and Edge 1996, 866-867) This flexible view of SST is mostly compatible with both the perspective of SCOT and that of ANT. In contrast, it is completely at odds with both the technological determinist linear model and the social determinist linear model. What is unique to SST is that it enriches the potential causes of the variation and convergence of technology beyond

visible social groups and actors, by taking structural and historical context into consideration.

Thus, the SST perspective seems to be the broadest and most balanced theoretical approach. However, this may reduce the sharpness of the perspective, that is to say, because the SST perspective takes more factors into consideration, it is more difficult to decide what is the most important based on the perspective. Despite this dilemma, in order to understand technological change, I think it necessary to tolerate this ambiguity, because what is the most important factor in technological change does not seem to be a question that can be given a single general answer. On the contrary, this position may go further: the social shaping of technology is still limited by the word social. As Latour and Woolgar did in the second edition of their book (Latour and Woolgar 1986), I think that it is all right to remove "social" from SST: the shaping of technology. This is obviously very broad, maybe too broad. However, at least as a starting point of empirical investigation into technological change, it seems better to be free from the priority of the social.

2.1.5. Science and Technology

The relationship between science and technology is important here in two ways. First, it is often believed that technology is just the application of science. This is one of the core assumptions of the linear model of technological change. Second, technology studies often directly apply notions and theories developed by science studies to research on technology, as we can see in SCOT and ANT. Is there a problem here? In this section, we briefly examine the relationship.

Case studies and historical investigation of technological change revealed by the early 1980s that technology is not just applied science. Technologists have their own cultural resources. Technologists inherit a good part of their culture in non-verbal ways. Technologists actually use the findings and theories of science, but scientists also use the ideas and artefacts of technology. Scientific knowledge is often full of uncertainty when an invention is achieved, and the achievement of the invention

often reduces the uncertainty in scientific knowledge. (Barnes and Edge 1982, pp.149-150; Faulkner and Senker 1995, pp.26-29) The linear model regarding technology as applied science has been replaced by an interactive, symmetrical model. (Barnes 1982; Barnes and Edge 1982, pp.151-152; Pinch and Bijker 1987, pp.19-21; Faulkner and Senker 1995. pp.27-29)

This parallel between science and technology can be used to justify the application of science studies to technology studies, in particular, within sociology. (Faulkner and Senker 1995, p.29) Recent studies including some historical studies of technological change, however, tend to highlight the distinctiveness of technology from science. This is not a return to the linear model. Given the horizontal, interactive relationship between science and technology, their differences are stressed. (Faulkner and Senker 1995, p.27, pp.29-34) Faulkner and Senker (1995) identify three closely related areas in which technology is distinguished from science: purpose or orientation; sociotechnical organisation; and cognitive and epistemological features. In purpose, technology is more practice-, or artefact-oriented than science. In organisation, technology is more structurally organised. In cognitive and epistemological orientation, technology is more design-oriented, more heterogeneous, more local and more tacit. (pp.31-34)[3] However, they are sceptical about the claims that science is more theory-based and technology more empirical, and that scientific theory is closer to mathematical theory and technological theory is closer to phenomenological theory. Hamlin (1992) also indicates that in technology material constraint is more significant than in science, that in technology people do more than what they know scientifically, that technological knowledge is dispersed among a greater number and diversity of people, that in technology solutions sometimes search for problems, that technology inherently intervenes in the world and the change is irreversible, and that it is impossible to imagine a final optimised technology. Pavitt (1987), too, argues that technology is more specific, more complex, more tacit, more cumulative and more expensive than science. Historical studies of technological change such as Constant (1980), Vincenti (1990) and McKelvey (1996) demonstrate these distinguishable characteristics of technology. Thus, these works emphasise that

[3] This is, again, to some extent the case in science. (Collins 1992)

science and technology are closely interactive but distinguishable. This view is also shared by proponents of SST, who argue that technology studies require more than just the application of science studies. (See Section 2.1.4) This is why the SST proponents insist on taking the historical and social context into consideration. Given the described differences between science and technology, SST seems to be most suitable perspective on technological change. However, the SST perspective excludes neither SCOT nor ANT perspectives. Both SCOT and ANT perspectives are as useful as historical, structural, and institutional perspectives.

Technological studies should be more than an application of science studies. But, this does not mean that the application of science studies to technological studies is not useful. On the contrary, it is still very useful. Although SCOT and ANT apply science studies to technology studies to some degree, we may be able to take it further. MacKenzie (1996b) suggests that we apply the sociology of (scientific) knowledge to understand the (functional) properties of artefacts, for example, whether artefacts work, how well they work and how safe they are. Knowledge about the properties of artefacts is part of knowledge, which is defined as any shared belief system, not necessarily correct belief by sociologists of knowledge. (MacKenzie 1996b, p.248) He insists that the general means for obtaining knowledge, namely, authority, induction and deduction, are also applicable to the knowledge about the properties of artefacts. That is to say, we can know the properties of artefacts by authority (people whom we trust tell us the properties), by induction (we learn the properties by testing or using artefacts) and by deduction (we infer the properties from theories or models), but none of these can guarantee the correct properties of artefacts, as is the case in any other knowledge creation. Authority may lose people's confidence. Testing conditions may be crucially different from conditions of use. Conditions of use are so complex that we cannot know exactly the properties of artefacts. Real conditions may be different from the ones that are assumed in theories or models. In addition, deduction is also accompanied by inference and trust, both of which are socially conditioned. MacKenzie argues, therefore, that our knowledge of the properties of artefacts is socially contingent, that controversy over the properties of artefacts is pervasive in technological change and that knowledge of the properties

of artefacts is no less social even when there are no such controversies to be seen. (MacKenzie 1996b, p.263) This thought underpins the idea that technological change is not linear even if it appears linear. However, intellectual effort is required to reveal this. About this, MacKenzie suggests that only historical analysis makes it possible for us to see how we were able to take for granted the knowledge of the properties of artefacts we now take for granted. (MacKenzie 1996b, p.263)

2.1.6. Linear Model Still Exists!

As we can see in the sections above, the linear model has been criticised by various disciplinary groups of social scientists. Rothwell (1995) suggests five generations of innovation model: technology-push model as the first generation (1950s - mid 1960s); market-pull model as the second generation (late 1960s – early 1970s); "coupling" model as the third generation (mid 1970s – early 1980s); integrated model as the fourth generation (mid 1980s – 1990s); and system integration and network model as the fifth generation (1990s -). Among them, the first two can be seen as the technological determinist linear model and the social determinist linear model. This clearly suggests that the linear model of technological change is being regarded as obsolete.

However, the linear model, especially its technological determinist version, still persists as a policy driver and as a standard model in several specific industries. Tait and Williams (1999, 2) suggest four reasons why the linear model has been resilient in the minds of policy makers: first, some policy makers are still unaware of its reputed problems; second, it is attractive as a metaphor for policy makers who want a simple understanding of technological change; third, existing policy repertories based on the model are well-entrenched in the minds and relationships of policy makers; fourth, the model matches the interests of academic research scientists and some research councils because it justifies the expenditure of large amounts of public money on basic research. (E. g. "Government focuses on science base," *Financial Times*, July 26 2000) Tait and Williams (1999, 2-3) indicate that a revised version of the linear model, named the "linear plus" model, has emerged. The "linear plus"

model stresses the relationship between academia and industry and the cooperation between various disciplinary groups, though it still assumes linearity from research to market.

The linear model is often regarded as reality in several exceptional industries such as the chemical industry (Cadogan 1997, 938) and the pharmaceutical industry. Fleck (1996, 14) writes, "In practical terms [the linear model] is applicable to situations characterised by a mature market structure and the presence of a scientific research intensive infrastructure, as is found in biotechnology and pharmaceuticals." Faulkner and Senker (1995, 211) also state, "pharmaceutical innovation conforms more to the linear model." This view is also reflected in the word "pipeline," which is often used in the pharmaceutical industry as below:

> SmithKline Beecham will today announce it is buying rights to a cancer drug as part of continuing efforts to improve its *product pipeline*. ("SB and Glaxo take stock of drugs' cabinet," *Financial Times*, 25 July 2000)
>
> Yamanouchi's formidable *R&D pipeline* is its engine of future growth. (Yamanouchi, *Annual Report 1999*, p.4)
>
> BMS is confident it has enough in the *pipeline* to more than offset any shortfall. ("Bristol-Myers remedies scepticism," *Financial Times*, November 29 1999)

The linear-model-like appearance of the pharmaceutical industry is created by regulation in the industry to a considerable degree. (Tait and Williams 1999, 8) Each step of research and development (R&D) process of pharmaceuticals in modern society is strongly regulated by the government. Without satisfying requirements of the current stage, the pharmaceutical company cannot advance its drug to the next stage. In sum, the linear model of technological change has been criticised by various disciplines of social science. But, in the practical world, it is still believed and used. In particular, even social scientists who in general criticise the linear model seem to believe that it is still applicable to a few industries including pharmaceuticals.

The claims that technological change in the pharmaceutical industry is like the linear model, however, do not seem to be based on detailed study on the innovation process. Therefore, it is still questionable whether the R&D process in the pharmaceutical industry is truly the one that is described by the linear model. This question gives us an opportunity for re-evaluating the linear model as one perspective on technological change. This question is also practically important because the pharmaceutical industry is one of the key industries for such countries as the UK, the US and Japan. It may have further significance when we consider that the industry may represent a group of "research-intensive" industries, which are expected to sustain economy and culture in "advanced" countries. Therefore, to answer the question, "Is it the case that the linear model of technological change can at least be applied to the pharmaceutical industry?" is an excellent challenge in attempts to understand technological change in modern society. And this is the objective of this research. I try to find an answer to the question by examining some cases of the R&D process in the pharmaceutical industry in detail. However, before we move to case studies, let us glance at the general characteristics of the pharmaceutical industry and the literature on it.

2.2. Research and Development in the Pharmaceutical Industry

2.2.1. Visiting Laboratories[4]

The first room This room is well lighted and partitioned into booths by frosted acrylic boards. Science equipment is crammed and piled into quite a large booth. Perhaps these machines are used for measuring or analysing chemicals. Most of them seem to be computerised. Machinery analyses chemicals and the display conveys the results to people. There are, however, few people apart from us. Maybe it is because strangers are looking at the laboratories. Maybe it is because it is not the time to check the results. Anyway, the laboratory is not an automation system, because each machine looks separated, unconnected to others. Each machine, however, looks very expensive. In fact, they are expensive, according to the director who shows us the laboratory. I have been hearing continuous sounds of motors and compressors. In the

[4] This visit to the laboratory, which was located in England, was conducted on 15 February 2000.

next booth, I can smell chemicals. I see several ordinary refrigerators. There are also a number of bottles of chemicals on racks, cupboards and laboratory benches. They are neither very tidy nor a mess. Then, there are several smaller booths, which look like personal offices. Women are not in the minority. The next booth is again full of science equipment and personal computers. Various logos of makers on the machines, but most of them are unfamiliar. Then, we go out of the room. There are a lot of doors before we get to the next room.

The second room This room is dark. A female researcher sitting in front of a sophisticated microscope and a display beside the microscope demonstrates how to use the apparatus to us. On the display, we can see a part of a cell. According to her, they can analyse a microscopic image on the computer screen by dying different proteins within cells with different colours. When she chooses a particular colour, we can see the distribution of a particular protein in the cell. It is said that the microscope can secure images every thirty seconds. If you get interested in a movement of proteins inside the cell, you can reconstruct images. You can also analyse the movement because it is digitally coded. You can download the data into a disk, and bring it with you and observe the movement anywhere you can open your laptop computer. Because it is digital, you can erase visual noises so that you can get a clearer image than with an ordinary microscope. The researcher explains everything cheerfully and proudly. The software of the apparatus looks very specialised and customised, and the operator seems to be well accustomed to it. It is said that they bought the software but they also modified and improved it.

The third room This room is well lighted, again. In the centre of the room there is a large table with a large, transparent plastic box on it, which occupies quite a large part of the space of the room. The box is very roughly 30 feet in length, 10 feet in width and 6 feet in depth. In the box, a robot is working. The robot does not look very flexible. Its thee-dimensional motions are rectilinear. The robot first picks up a sample case from the storeys of them at the end of the box. Then it takes it to a bar-code checker. Then it takes the case to the point where some sort of reagent is put in the samples. Finally, the robot takes the case to an analyser. And then, it goes back

and repeats these motions. This equipment is connected to a computer and the results of analysis can be seen on the display. By the side of the plastic box, there is a set of red, amber and green pilot lamps, which are often seen in a modern factory. But there is neither the loud noise nor the alarming music you can hear in the factory. On a bench by the wall, there are a lot of things: pipettes, sample cases, something looking like an electronic thermometer, a roll of sellotape, a pair of scissors, papers, a calculator and so on.

2.2.2. Talking with Researchers in the Pharmaceutical Industry[5]

Interview A

Mr A is a chemist, Japanese, male and 39 years old. I hear about his daily life at the laboratory.

> Hara: What do you do in an ordinary day?
>
> Mr A: I do almost the same things every day. There's a target compound, but of course I can't get it all at once. So, I do that step by step and day by day. Each step includes reaction, purification and isolation, and then I go on to the next step. I can get a target only after I repeat this a lot of times. So, this is what I do every day. Each chemical operation is basically the same as what students do at the university. What I do in spare moments away from these chemical operations is thinking about what sort of compound I should make next, or investigating what other researchers are doing either from reading in the library, or from discussion with my colleagues.
>
> Hara: Are you working alone?
>
> Mr A: Yes, normally, one chemist is working on one compound in the early stage of research. I mean the one compound includes its analogues and derivatives. When it becomes clear that the work requires more manpower, or that we must hurry, our boss decides to attach more people to the work and organise them by the division of labour. But at first, when it is unclear whether the compound works or not, one chemist does all tasks related to it.
>
> Hara: What kinds of instruments do you use in your research? I guess that you are working with test tubes, beakers, and so on. Am I right?

[5] These interviews were conducted on 8 November 1999.

Mr A: Yes (laughs). These days, we have a specialised section using the combinatorial chemistry [the robotic equipment for high-speed chemical synthesis]. But our section is using the same kinds of glass instruments as were used several decades ago. We add reagents to chemicals in test tubes, heat it or just stir it, and observe the result. I'm afraid we don't see any progress in these operations. What is different from the old days is that reagents improve in variety and in quality. The control of temperature of a heater is much more accurate than before. But what we are doing is basically the same.

Hara: How long do you spend on discussion in a day?

Mr A: Well, I may have no discussion and concentrate on experiments all day long. Or I may spend more than half a day on discussion. It depends. When I was young, I spent most of my time on operations. But as I get older and begin to take the initiative in research, I spend longer on discussion. I am in discussion not only with chemists but also with biologists who conduct bioassays or animal experiments over the results of the biological tests.

The following question and answer shows us the typical difference between academic research and industrial research.

Hara: Do you publish the results of your research?

Mr A: Yes, well, if I can get permission. To publish research, we have to get permission from our company. We can't make all of our findings open to the public. When we find something to be developed, we file for its patent as soon as possible. Even after we secure the patent, it is often forbidden to publish the findings for a while.

Interview B

Dr B is a pharmacologist, Japanese, male and 41 years old. Again, I hear first about his normal everyday activities. Here, we can see the characteristics of meetings in pharmaceutical research laboratories. We can also hear him talking about the flow of drug R&D.

Hara: What do you usually do every day?

Dr B: Well, it's different now from in the past. I've been a research manager since last year, so I'm not doing animal experiment now, except on the occasions when I am asked to help. I'm usually working in the office. I'm now in charge of two projects. One is a drug for arteriosclerosis, and another

is a drug against blood clots. My task is to supervise the progress of these research projects. So, mostly my present job is a desk job.

Hara: Do you have a lot of meetings?

Dr B: Yes. Every day, there are one or two, one in the morning, another in the afternoon. Some meetings are informal and small. Some are formal.

Hara: Who attends the meetings apart from you?

Dr B: Well, so, at the most informal level, I meet my subordinate researchers and listen to their reports. I, in turn, report the progress of the projects to my bosses at the higher-level meeting.

Hara: Do you have meetings with chemists, manufacturing experts or marketing staff?

Dr B: Yes. There is a flow in the evaluation of compounds, though it depends on the theme of projects. Chemists synthesize compounds and then we pharmacologists assay them and produce the results. The chemists examine the results and synthesize the next bunch of compounds. Chemists and pharmacologists repeat this many times. At that stage, we meet chemists each time the results come up, plus regularly, for example, once a month. At the later stage, when we need mass production of a compound, we have meetings including people synthesizing it on a plant level scale. But most of our meetings are related to the earlier stage.

Hara: Don't you have meetings with marketing staff?

Dr B: Yes. Several problems usually arise in the process of development of a drug, even in the process of its clinical trials. On those occasions, we are asked for our opinion by the staff of the development division, and we respond to them. If telephone or e-mail is good enough, it's OK. But sometimes meetings are necessary. We sometimes hold them in our laboratories, and are sometimes called to come to headquarters.

Dr B talks to me about how the methods of drug research have changed recently.

Dr B: Before, the mechanism of action of a drug was often revealed after the drug was found to be effective. We had to find an explanation as to why the drug worked. Nowadays, we first speculate about the mechanism of action and a related gene. To confirm that, we can make the mice without a specific gene or ones which are apt to activate a specific gene. By using the mice, we can find out whether the gene is related to the disease. So, nowadays, it is becoming more common that the drugs whose mechanisms of action are clearly known are developed clinically. It is also getting harder to obtain the approval of regulators without a clear explanation of the mechanism of action.

... When we want to exploit a new mechanism of action, we propose it to the board of the research division. If they approve the proposal, the specialised department does the mass screening of hundreds of thousands of compounds in the compound library[6] by using robots. Even though the idea is very good, the screening often hits nothing in the library. If, by good fortune, it hits one or a few compounds, we examine the compounds in cells. If we confirm the results, we then ask the chemistry department for further synthesis of its analogues. Amongst these analogues, we choose the most potent compound.

Hara: Where do you get your new ideas?

Dr B: Formally, we get information from academic conferences and literature, but that's often too late. So, we get information directly from academic researchers we get acquainted with at conferences, by keeping in touch with them. Especially, being in contact with leading scientists is very helpful because they know where are the frontiers of each research area and what kinds of research are accepted in leading academic journals before they are published. In reality, however, it depends on research areas how much we can get information in this way. And, of course, we have to offer our original information to the academic researchers if we want to get some from them. Without that it doesn't work.

2.2.3. Formal Process of Research and Development of Pharmaceuticals

In this study, I deal with the innovation process of prescribed drugs. Prescribed drugs, or ethical drugs, are normally given to patients either by pharmacists based on the prescription issued by doctors or directly by medical practitioners in hospitals and clinics. Large pharmaceutical companies earn most income from their prescribed drugs. (Davis 1997, p.8; The Association of the British Pharmaceutical Industry 1997, p.13; Japan Pharmaceutical Manufacturers Association 1997, I-5) Almost all major product innovations in the pharmaceutical industry are those of prescribed drugs. To secure profits from novel prescribed drugs, pharmaceutical companies file patents for new compounds, often together with their analogues and derivatives, immediately after they discover the compounds and their potential clinical applications. Therefore, newly discovered prescribed drugs are sometimes called patented drugs. These drugs are normally given brand names on the market. This is why they are also called

[6] A compound library is a collection of compounds possessed by a pharmaceutical company. Pharmaceutical companies collect the compounds through their own research or by acquisition from other organisations. It is said that each large pharmaceutical company has a compound library with hundreds of thousands of compounds. (Thomke, von Hippel and Franke 1998, 324)

brand-name drugs, in contrast with generic drugs, which are marketed by other manufacturers after the relevant patents have expired.

Most prescribed drugs currently used work through their interactions with receptors within our bodies. The human body, as well as other animals' bodies, is regulated by various chemicals, such as hormones and neurotransmitters. These chemicals are used for communication between different cells and different organs in the body. On the membrane around cells, there are a lot of special proteins called "receptors." There are also some types of receptors inside cells. Each receptor catches a specific kind of hormone or neurotransmitter as if they were a lock and a key, and then sends a specific signal inside the cell, which will cause the cell to respond in a specific way. (Stone and Darlington 2000, pp.1-10) Drugs combine with these receptors and promote or inhibit the reaction of cells. A drug which has the same actions as a natural hormone or transmitter is called an agonist or stimulant. Normally, a clinically used agonist possesses stronger potency and/or longer duration of action than a natural hormone or transmitter. In contrast, a drug which inhibits the actions of a hormone or transmitter is called an antagonist or blocker. Although agonists and antagonists of the same receptor have opposite functions, their molecular structures are often very similar, because they have to combine with the same receptor. (Patrick 1995, pp.61-63) All of the drugs I examine in the case studies in this research belong to this type of drug, except mevastatin and cefotiam which inhibit specific enzymes in the body or bacteria cell walls, and nicardipine which blocks specific channels (also made by proteins) in the cell walls. There are also other types of drug, which target transport enzymes, nucleic acids and specific types of cells such as cancer cells. In the near future, drugs of which the targets are specific genes are likely to appear. (Stone and Darlington 2000, pp.12-13) All drugs have potentially harmful side effects partly because chemicals within the body normally play more than one role, partly because they have to be metabolised, that is to say, be transformed into other chemicals, which may have toxic effects within the body, and partly because the body sometimes rejects strange chemicals (allergic reaction). Prescribed drugs are normally more potent than non-prescribed, so-called over-the-counter drugs, but, at the same time, potentially more dangerous because their side effects are often

stronger. This is one of the main reasons medical and regulatory authorities in modern countries strictly control the manufacturing and distribution of prescribed drugs, although it is not the only reason. (Abraham 1995, pp.36-86; Davis 1997, p.120)

R&D in the pharmaceutical industry is conventionally split into two stages: "research" and "development." According to the conventional view, research activities in pharmaceutical companies are aimed at the "discovery" of drugs, whereas development activities mainly refer to clinical trials. (Chiesa 1996) A drug discovery is defined as a discovery of the "fact" that a natural or synthesised chemical has a profile of biological activity which can be applied for the treatment of diseases. The "fact" does not necessarily include a clear explanation about the action mechanisms. Until recent times, drugs were able to be approved for use without a clear explanation about the mechanisms. Nowadays, this is more difficult, as we can see in *Interview B* above, but even so, there must still exist potential uncertainty about the mechanisms. Strictly speaking, therefore, the "fact" is a system of beliefs. (Barnes, Bloor and Henry 1996, pp. 69-73; MacKenzie 1996b, p.248) Sometimes, a drug discovery is regarded as a discovery of a chemical which has a profile of biological activity, but this view may be misleading, because the chemical is often not naturally occurring, but intentionally synthesised. Invention is a more appropriate word here and should be distinguished from discovery. In this research, however, I use the word "discovery," referring to the first learning of the causal relationship between the chemical and the biological activities, not to the chemical itself. My using the word discovery implies no ontological commitment to the correspondence between that learning and reality.

Both chemists and biologists play a core role in the research process and that the interaction between the two disciplines is the key to the achievement of drug discovery. However, it should not be ignored that other disciplines such as physics, mathematics, statistics, computer sciences, electronics, mechanical engineering and material engineering also support the process of drug discovery, as we can see in the "laboratories" in Section 2.2.1.

After a drug discovery, the compound is examined in detail by using different animals. The toxicological, pharmacological and pharmacokinetic properties of the compound are investigated. This process is often called pre-clinical tests or pre-clinical development. At this stage, initial studies on the production process of the compound start, because it is necessary to supply a larger amount of the compound for clinical trials and the development of preparations. (Pisano 1997, p.122) Development of preparations is more important today than before because now the notion of drug delivery systems is taken seriously into consideration. (See Chapter 6) If the data of the pre-clinical tests are favourable, the compound goes into clinical trials. Before that, however, a managerial decision is made because clinical trials require an enormous amount of money. Also, an approval by the regulatory body is needed, because clinical trials use humans. (McIntyre 1999, p.73; The Ministry of Health and Welfare 1996, pp.85-105)

Clinical trials before marketing, which are conventionally a synonym of drug development, are normally divided into three phases. In phase I, a drug candidate is given to healthy volunteers to investigate its toxicological and pharmacological profiles. In phase II, the drug is given to a small number of patients at various dosage levels and with different dosage forms in order to examine its efficacy and safety, and to determine the appropriate dosage profiles. In phase III, the drug is given to a much larger number of patients at multiple sites for quite a long time in order to confirm its efficacy and safety. The trials in phases II and III are normally controlled and the drug is compared with a placebo and/or an existing major therapy. (Chiesa 1996, 693-640; Pisano 1997, p.119, pp.123-124) The governmental authority strictly regulates these phases of clinical trials. Phases can be overlapped with the permission of the authority but cannot be waived. This regulatory system of clinical trials has been constructed in particular since the disaster caused by thalidomide in the early 1960s. The relevant institutional changes happened first in 1962 in the US, and around 1967 in the UK and Japan. (Temin 1980, p.125; Abraham 1995, pp.66-74; *Nihon Yakushi Gakkai* ed. 1995, p.132; Kaufer 1990, 154; Timmermans and Leiter 2000, 45-46) Most of the drugs I will examine in case studies in this research

experienced these phases of clinical trials. It is also important to notice that clinical trials are conducted by a number of doctors and patients who are outside the control of the pharmaceutical company. Factors such as protocols, organising doctors, schedule management and informed consent are necessary. (Smith 1985. pp.80-88) Statisticians also play a significant role in clinical trials because results of controlled studies are statistically analysed and interpreted. (Marks 1997, pp.129-248)

As a matter of course, a drug must be produced on a much larger scale than the laboratory level before the large-scale clinical trials and commercialisation. Therefore, process development must be done between the discovery of a drug and the large-scale clinical trials. A specialised process R&D group in the pharmaceutical company normally conducts this function in parallel with product development. Process development is not a once-for-all sort of activity, but a continuing effort. Each stage of pre-clinical and clinical studies requires a certain amount of the drug. At each moment, the production of the required amount of the drug must be achieved, even if the process is far from the optimum one for large-scale production. Regarding the values in process development, cost reduction is in general important. However, reduction of development time is also important especially in the pharmaceutical industry because it may constitute the bottleneck of the whole process of drug R&D, which is crucial in terms of competition in the market. Flexibility is also required because changes of product profiles often arise in the process of drug development. (Pisano 1997, p.81, pp.95-102) Process development includes identification of a lot of alternative routes of synthesis and selection of the best route among them in terms of quality, safety, simplicity and costs. It also includes high uncertainty because scaling-up means the entry of further heterogeneous factors, both the material and the social. (Pisano 1997, pp.125-134; Smith 1985, pp.111-116) Human actors such as chemists, chemical engineers, system engineers, electricians, mechanics, operators and managers play a role in a plant. Non-human entities such as tanks, pipes, censors, thermometers, pressure gauges, cables, computers, software, terminals and clocks also play a role.

When clinical trials and process development of a drug are successfully completed, the manufacturer applies for the approval of its manufacturing and marketing to the regulatory body. The application requires the detailed results of pre-clinical tests and all clinical trials, detailed description of the clinical protocols, statistical analysis of the results, expert opinions on the data, detailed description of the manufacturing process and other prescribed data and analysis. (Pisano 1997, pp.124-125; Reich 1986; The Japan Ministry of Health and Welfare 1996, pp.127-206) When the regulatory body approves the application, the company can "basically" launch the drug. The word "basically" is used because a further procedure may be needed in some countries. In Japan, for example, without obtaining an official price determined by the Ministry of Health and Welfare, it is virtually impossible to sell the drug in the country. (Reich 1986, 23; Campbell and Ikegami 1998, p.154) It is reported that the whole process of R&D of a drug except the research before the discovery took more than 10 years and cost more than $350 million in the early 1990s. (Weisbuch and Moos 1995, 244)

Thus, the formal R&D process of a drug consists of a number of stages: very roughly, research, pre-clinical tests, clinical trials (phase I, II, III), process development in parallel with product tests, and filing. The R&D process of a drug is strictly regulated by the governmental authority stage by stage. Given the regulation and huge investment required in the later stages of development, the management of pharmaceutical companies also strictly controls the progress of the R&D process by the milestone approach. This explains why the R&D process in the pharmaceutical industry is regarded as similar to the linear model. It can be schematised as in Figure 2.2.

Figure 2.2: Formal Drug R&D Process Schematised by the Linear Model

<table>
<tr><td rowspan="2">Research
Drug
Discovery</td><td rowspan="2">→</td><td>Pre-clinical
Tests</td><td rowspan="2">→</td><td>Clinical
Trials</td><td rowspan="2">→</td><td rowspan="2">Application for
Approval</td><td rowspan="2">→</td><td rowspan="2">Marketing and
Sales</td><td rowspan="2">→</td><td rowspan="2">Use</td></tr>
<tr><td colspan="3">Process Development</td></tr>
</table>

However, even though the formal R&D process can be schematised in a linear process, there is a question of whether this is the case in the real process of drug R&D. To what extent do previous studies answer the question? How do they deal with the process of drug R&D? We will review the relevant literature in the next section.

2.2.4. Literature on Technological Change in the Pharmaceutical Industry

Because innovation is a crucial problem for the pharmaceutical industry, many researchers in economics and organisation studies write on innovation in the pharmaceutical industry. In contrast, literature on this topic by sociologists seems to be limited in number.

2.2.4.1. From the Economic Viewpoint

According to Comanor (1986), there are three strands in economic studies of R&D in the pharmaceutical industry, namely, the determinants of research expenditure, scale economies in R&D and the costs and returns from R&D. On the determinants of research expenditure, factors including firm size, research productivity, product diversification, the level of internally generated funds, the level of research and the direction of research have been suggested as determinants of research spending (Comanor 1986, 1190-1191).

On the scale economies in R&D, there is disagreement among researchers about whether larger pharmaceutical companies have an advantage in innovation over the smaller ones. Comanor provides two alternative views about this: the disagreement may be due to the difference of the periods of data collection; or maybe due to the definition of innovation, that is to say, "larger firms are relatively more important when all new drugs are included but not so in regard to the most important innovations" (Comanor 1986, 1192-1193). However, more recent studies tend to support the importance of firm size for R&D productivity (Jensen 1987; Thomas 1990; Alexander 1996; Henderson and Cockburn 1995). Jensen (1987) and

Alexander (1996) argue that increase of firm size does not affect or possibly negatively affects the marginal productivity of R&D while it positively affects the average R&D productivity. Henderson and Cockburn (1995) argue that economies of scope are as important as the economies of scale *per se*. Two different but related economies are included in their economies of scope. One is from the 'free-riding' effect among different research projects based on the public goods aspect of knowledge; the other is from internal spillovers of knowledge between projects that benefit each other.

On the problem of whether the returns generated by R&D are sufficient to cover their cost, a body of literature by the mid 1980s indicates that the average returns for new drugs have declined and may be less than average development costs in recent years. (Comanor 1986, 1195) Diminishing average returns in the pharmaceutical industry is also indicated in more recent works. (E.g. Alexander, Flynn and Linkins 1995) Comanor, on the other hand, points out that the returns from a small number of very successful products are now especially critical to success in this industry (Comanor 1986, 1195). This also seems to be consistent with the results of more recent studies. (Grabowski and Vernon 1990; Grabowski and Vernon 1994, 398-400)

There seem to be two more strands of research on the economics of R&D in the pharmaceutical industry. One strand is concerned with the effects of regulation on innovation, in particular, on the R&D productivity defined as the number of new chemical entities discovered and introduced in market per R&D expenditure. While Grabowski, Vernon and Thomas (1978), Wiggins (1981) and Jensen (1987) suggest the negative effect of regulation on innovation, Thomas (1990) later argues that the larger US pharmaceutical firms benefited from FDA regulation due to reduced competition though smaller firms suffered reductions in research productivity because of regulation. The other strand of research is on the general trend of decline of research productivity. Henderson and Cockburn (1995) and Gravis and Langowitz (1993) can be categorised into this strand.

These works on the economics of R&D in the pharmaceutical industry indicate that there seem to be economies of scale, economies of scope, the declining trend of return, the declining trend of research productivity and the effect of regulation in the pharmaceutical R&D. Although quantitative relationships between various empirical data related to technological change in the industry are shown by these studies, the process of technological change remains untouched.

McKelvey (1996) is, however, an exception. Although it might be inappropriate to classify her work into the economic literature because she declares that her approach is multi-disciplinary (p.298), I put it here because it is more closely related to "evolutionary economics" established by economists of technological change including Nelson, Winter and Dosi, than organisation studies of technology and innovation or sociology of technological change. She argues that a fundamental assumption of evolutionary economists that technological change is evolutionary has been little examined in detail by empirical studies. (p.257) She, therefore, shifts the focus of research from innovations as objects to those as processes (p.2) and examines a case history of R&D process of genetic engineering, in particular that of human growth hormone made with recombinant DNA techniques (rDNA hGH) as her empirical base. She identifies in the process various agents, including academic scientists, biotech firms, established pharmaceutical companies, governments, doctors and general public. She describes the shifts of knowledge-seeking activities of these agents from scientific to scientific-economic and techno-economic environments, with the advance of the process towards practical uses. She concludes that the innovation process of rDNA hGH is more accurately described as evolutionary, that is to say, including the dimensions of diversity, retention and selection through the complex interactions among these agents and among agents and environmental conditions, rather than as linear, which appears to be the case on a hasty reading. (pp.26-36, p.258) She also emphasises the cross-stimulating relationship between science and technology. This relationship became more obvious when the knowledge-seeking activities of agents entered scientific-environment and techno-economic environments. In particular, she emphasises the importance of production, where interaction between science and technology is very crucial, in the

process of biotechnological innovation. (pp.291-294) Thus, McKelvey's work is especially close to my interest, and partly answers my question about the linearity of the drug R&D process. However, her answer is still insufficient in several points. First, her work does not include sufficient examination of the social process of drug R&D inside organizations. Second, the economic aspect of social processes is particularly emphasised, whereas sociological and political aspects are only briefly inspected in her study. Third, her work is based on only one area of pharmaceuticals. The area is relatively new area in the pharmaceutical industry and may be problematic to be regarded as a representative area. Although her conclusions seem quite convincing, it is necessary to examine them through further detailed case studies with a more balanced viewpoint. Literature from organisational and sociological viewpoints below seems to be helpful in this regard.

2.2.4.2. From the Managerial and Organisational Viewpoint

Most of the recent works on the management and organisation of the pharmaceutical industry highlight R&D and innovation, because they are regarded as the critical factors of competitive advantage. I roughly categorise the discussions here into three: discussions on the technology strategy; on the networking for innovation; and on the management of research organisation.

Discussions on technology strategies in the pharmaceutical industry tend to identify trends of technology as a crucial environmental factor and then discuss the strategy. Bogner (1996) identifies several technology trajectories and other trends of technology in the history of the US pharmaceutical industry. He identifies, for example, the organic chemistry trajectory (p.54), the anti-infectant research trajectory (p.59), trajectories of non-antibiotic drugs (p.82) and the trajectory related to biotechnology (p.117). Then he examines strategies of pharmaceutical companies and identifies several strategic groups characterized as "traditionally antibiotic," "broad organic-chemistry focus," etc. in the 1970s, and "narrow focus research firms," "broad focus research firms," "genetic firms," etc. in recent years (pp.142-144). Achilladelis (1993) focuses on the sector of antibacterial medicines, and from

the historical analysis, identifies four technological trajectories in the sector, namely, sulphonamides, natural product antibiotics, semi-synthetic antibiotics and synthetics. He also found corporate technology traditions in several companies. The concept of a corporate technology tradition, defined as the "concentration of a company's R&D resources on a particular technology for a very long period of time leading to the introduction of many innovations embodying this technology" (p.281), implies that there may be further diversity of company strategies in a single therapeutic area. Hara (1997) identifies similar trajectories and corporation technology traditions in the development of antibacterial drugs in Japan. Galambos and Sewell (1995) identify four scientific and technological cycles in vaccine development. Many authors notice the impact of biotechnology on the pharmaceutical industry (E. g. Sharp 1991; della Valle and Gambardella 1993; Whittaker and Bower 1994; Gambardella 1995; Otero 1995; Sharp1995; Zucker and Darby 1997), and many writers including Gambardella (1995), Whittaker and Bower (1994), Zucker and Darby (1997) relate it to the discussion of strategic linking and networking. These studies can be regarded as being based on the softer version of technological determinism because they implicitly regard technological trajectories as an environmental factor. Sapienza (1997) regards the strategy based on technological trajectories as a shaping activity. (p.26) She regards technological trajectories as the results of overall R&D as well as program- and project-specific decisions. And she argues that technology strategy is the blue print for the technology trajectory. (pp.5-7). Thus she seems to most explicitly regard technology trajectories as being shaped by organisations.

The research on the external linking and networking of pharmaceutical R&D for innovation is probably the most flourishing area in the organisation studies of the industry. Most works in this area discuss it with reference to biotechnology. Whittaker and Bower (1994) show that the R&D alliance between pharmaceutical companies and biotechnology companies increased dramatically in the 1980s. They argue that this is not temporary but long-standing because their relations shift toward functional specialization. Gambardella (1995) also points out radical change in the pharmaceutical R&D associated with the development of biotechnology and

molecular biology, and its implication for the division of labour between the large pharmaceutical companies and small-to-medium-sized biotech companies, universities and other research institutions. He argues that because scientific capability embedded in individuals is often the critical resource for drug discovery on the one hand, and because the commercialisation of drugs needs solid financial and managerial capabilities on the other, the division of labour between small organisations with the former capabilities and large organisations with the latter capabilities is very hopeful (pp.163-164). Faulkner and Senker (1995) identify changes in the relationship between the pharmaceutical industry and public sector research (PSR) from the early era of biotechnology (1983-4) to more recent times (1990-1). They identify that the role of PSR in the linkage shifts from the somewhat informal and random one towards the more formal and specialized one under the growth and penetration of biotechnology in the industry. Powell, Koput and Smith-Doerr (1996) indicate that when the knowledge base of an industry is both complex and expanding and the sources of expertise are widely dispersed, as is seen in biotechnology, innovation will stem from organisational learning in networks, not individual companies. These studies argue that network-form organisations are appropriate and sustainable in the era of biotechnology-based pharmaceutical innovation.

Two more detailed studies on this issue provide us with rich information on the process of innovation. Zucker and Darby (1997) provide a case study of the transformation of a large incumbent pharmaceutical company by "the biotechnological revolution." In the study, they notice the following issues: senior management with the scientific ability to assess the technology championed the transformation; many scientists embodying biotechnology were hired; collaborations and joint ventures with university scientists and new biotechnology firms were used to improve internal expertise; the existing related knowledge made for more effective applications of biotechnology; the firm was able to hire star scientists. By detailed observation through a case study, they reveal that formal networking is insufficient to absorb the impact of biotechnology. Galambos and Sewell (1995) examine the history of vaccine development in the US pharmaceutical industry. The most

remarkable feature of this work is that they regard drug developments as consistently being accomplished through networks. They identify four cycles in the history of vaccine development, namely, the bacteriology cycle, the virology cycle, the cycle associated with the new bacteriology of polysaccharide capsules and the cycle grounded in biotechnology and molecular biology. According to them, new cycles were accompanied with new science and medical networks and the vaccine companies sought to accommodate them. They argue that over time the networks have become more complex and differentiated both internally and externally. Thus, the historical investigation reveals that external networking did not begin in the biotechnology era, but had existed before that and that the era of biotechnology has brought a new arena for networking.

The third interest of the research on the management of pharmaceutical innovation is management of the R&D organization. The effective and efficient assimilation of external knowledge seems to be one of the most important issues there. Specialised scientific competence within the organisation is emphasised for evaluation and absorption of external knowledge. Gambardella (1995) argues that companies with better in-house knowledge assets in biotechnology use more intensively external linkages (p.165). Faulkner and Senker (1995, p.97) and Sapienza (1997, p.188) also emphasize the in-house assessment capability of external knowledge. Bierly and Chakrabarti (1996) argue that technology cycle time, from initial development to product launch, is shorter in internal knowledge exploitation than in external knowledge utilization. They argue that this is because the relationship between organisational learning and new product development is moderated by strategic flexibility, controlled by flexibility in manufacturing, finance and marketing, and the range of knowledge base. Fitzgerald (1992) indicates that the assessment process of external technology involves many functions, namely, pharmacologists, toxicologists, pharmacists, physicians, marketing, legal experts and representatives from the major international markets. This heterogeneity might make prompt organisational learning and accurate assessment much harder.

One of the other issues in the management of pharmaceutical R&D is the difference between research function and development function. Chiesa (1996) identifies several differences between research and development. According to him, research in the pharmaceutical industry is characterised by unpredictable timing, informality, modest expenditure and unpredictable results, while development is characterised by predictable timing, formality, huge expenditure, and planned results. He indicates that these differences result in difference between research management and development management. For example, research management has characteristics such as direct communication and pressure from a sense of urgency, while the management of development has characteristics such as formal communication and pressure on deadlines.

The literature on pharmaceutical innovation from the managerial and organisational viewpoint highlights the relationship between technological change and corporate strategy, the inter-organisational network as the key organisation form, the in-house scientific capability as the key factor for success in the pharmaceutical business and the differences between research function and development function in the industry. The studies show us some aspects of the process of technological change in the industry. However, the detailed interaction between various social and material factors in the process is not sufficiently described in these studies. In particular, social and political interaction within an organization, which has been described in several studies of other industries (Whipp and Clark 1986; Thomas 1994), has not yet been explored in this industry. Only several historical case studies such as Galambos and Sewell (1995) and Zucker and Darby (1997) provide us with some detailed aspects of the process of drug R&D.

2.2.4.3. From the Sociological Viewpoint

Despite the potential opportunities for sociological analysis, there does not seem to be much literature on technological change in the pharmaceutical industry from the sociological point of view. On the one hand, according to Bartley (1990), the sociology of medicine has traditionally been outside the construction of medical

knowledge. Rather, it has been concerned with the ways in which medical knowledge is applied. In particular, how medicinal technologies are developed and introduced into practice has often been viewed in a technological deterministic way. (Elston 1997, p.4) Recently, however, the advent of the sociology of scientific knowledge (SSK) and other strands of the sociology of science has extended the opportunity for sociology to investigate the construction of medical science and technology. This can typically be seen in the sociology of medical science and technology, which has recently emerged. (Elston 1997) Nevertheless, pharmaceuticals do not seem to be the dominant topic even in this area. They are at most one of the major topics there. In this section, we review several examples of the sociological studies closely related to the construction of pharmaceutical medicine.

Bodewitz, Buurma and de Vries (1987) analyse the drug regulatory process in which the efficacy and safety of the drug are adjudicated. They identify four social groups, each occupying a specific position in the social system of medical care and expressing a specific perspective on drug regulation practices: the general public, the pharmaceutical industry, the representatives of drug regulation agencies, and medical scientists and practitioners. They argue that in this social system no matter how present regulatory practices are evaluated, science provides the yardstick for assessing their rationality for all groups. However, according to them, the asymmetry between standards of efficacy (double-blind methodology) and standards of safety (no commonly accepted standards) gives room for the diversity of assessments and leads to a complex mixture of factual and value-laden judgements. They indicate that standards of safety evolved along different lines between the US and European countries: while the standards were developed somewhat voluntarily within established professional thinking in the US, in Europe they are brought about by outside pressure such as consumer organisations representing the general public. They conclude that scientific procedures and certified knowledge are also outcomes of the social process of acceptance.

Richards (1988) deals with the debate over the efficacy of vitamin C in the treatment of cancer. She compares it with cases of two other drugs, namely, 5FU and interferon.

According to her, whereas vitamin C was rejected by the medical society because of the lack of "sufficient" evidence of its efficacy for the treatment of cancer, the other two drugs were recognised as cancer treatment without the same level of evidence as was required in the former case. Moreover, the methods of the "crucial" clinical trials that showed the inefficacy of vitamin C were conventionally "rigorous" but fundamentally inconsistent with the theory and ideology of the proponents. Richards suggests that vitamin C was incompatible with the then established treatment of cancer, the interest of the medical authority, the interest of funding organizations and the interest of most of the pharmaceutical companies, whereas the other two drugs were more compatible with them. She concludes that the evaluation of medical therapies is inherently social and political and that this social character of medical knowledge cannot be eliminated by methodological reform: the randomised, controlled clinical trial, no matter how rigorously organised and operated, can neither guarantee objectivity nor definitively resolve controversy over competing therapies or technologies. (Richards 1988, 686-687)

Abraham (1995) also highlights drug testing. His interest is whether, and how, corporate bias may influence the scientific processes of evaluating the safety and effectiveness of a new drug (p. vii). He establishes a framework based on an explicitly realist sociology of scientific knowledge. However, he also integrates some conceptions which stem from relativist SSK strands ("strong programme", EPOR, constructivists, ANT). Moreover, he adopts some conceptions from Marxist studies, risk studies and the theories of the State and regulatory capture. He defines bias as "the advocacy/practice of claims/actions that are non-credible because they are inconsistent with the very scientific standards which the advocate/practitioner accepts as legitimate, and are convergent with identifiable interests/values" (p.29). He presumes (self) interests of profit maximization for the pharmaceutical industry, and of good health for patients. He also presumes that "rational" companies and consumers will pursue those respective interests. Based on several case studies, he indicates that bias exists among many industrial scientists; that the bias coincides with the commercial interests of the pharmaceutical company; that such corporate bias becomes entangled with some reward systems of science; and that the British

regulators are more biased than their American counterparts because of the close institutional relationship in the UK. Based on these findings, he insists on reform to reduce corporate bias.

Clarke and Montini (1993) examine how various actors were related to the construction of an oral abortion-inducing drug, RU486, by using "arena analysis." Arena analysis emphasises multiple views of various actors: it attempts to view the constructed world metaphorically over the shoulders of all the actors, rather than only of scientists and engineers. Thus, they identify various actors and their different views of RU486. For example, for reproductive scientists it is "the second generation pill." For family planning, population control and abortion provider organisations, it is a means of mobilising women to fight for new birth control. For pharmaceutical companies, it was a headache. For the clinicians who conducted its clinical trials, it was a means of "doing science." For medical groups, it is a means for greater safety in the practice of medicine and a means of fighting for medical autonomy. For antiabortion groups, it is another means of killing the child in the womb and a means of intentionally inducing a miscarriage. For feminist pro-choice groups, it is a means of mobilising feminists. For women's health movement groups, it is a means of safe abortion for some women who so choose. For some politicians in California, it was a strategy to become the governor. And so on. They conclude that a fuller and more historicized arena of the construction of technology can be obtained by following all these actors.

Prout (1996) describes the mutual constitution of the metered dose inhaler (MDI) and various human actors by applying actor-network theory. Although the MDI is not a drug, its actor-network seems similar to a drug's because it is used together with a drug. Prout identifies both human actors including patients, doctors, technicians and scientists, and non-human actors including aerosol gases, the Bernoulli principle, metering valves and the lung in the actor-network. He describes the interactions between these actors and transformation of the actor-network: configuring the users, anti-programmatic actions of users and modifications of the MDI. He argues that "ANT can help in understanding the intricate and mutually constitutive character of

the human and the technological in the processes and relationships of sickness and healing." (p. 214)

Epstein (1996) describes the social history of the production of biomedical knowledge, specifically, knowledge on the causation of and the treatment of AIDS. His approach is a synthesis of conceptions coming from the sociology of scientific knowledge, the social history of science and theories on social movement. In the analysis, he especially focuses on the role of lay people, in particular, that of AIDS activists in the formation of the biomedical knowledge. According to him, the role of the activists in the treatment controversy was greater than that in the causation controversy. He states that the activists have challenged the calculation of risks and benefits by the traditional experts such as researchers, doctors and statisticians, and have helped to change the rules governing the kinds of evidence required to determine the efficacy of AIDS drugs by becoming "lay experts." He argues that "analysts of science and medicine should attend to the strategies pursued by lay actors in their attempts to speak credibly about science and medicine"(p .332), because lay actors, as well as experts, can and do transform research.

Van Kammen (1999) examines the process in which the bodies of future users of anti-fertility vaccines have come to be represented by female bodies while the drugs have been researched and developed. Biological reasons are denied because both men and women can use the vaccines. Rather, specific material and political factors mainly constructed the presumed bodies of future users. For example, when immunologists searched for the target of the vaccines, the hormone called hCG gained from the placenta was highly available and ethically and politically less problematic, because they are regarded as being separated from human bodies. Spermatozoa were also easy to obtain and use for experiments. Both hCG and spermatozoa became the targets (antigens) of the vaccines. The female body contains both of them when the drugs work, whilst the male body contains only the latter. In addition, one of the anti-sperm vaccines caused an adverse side effect in the male. Moreover, in the choice of the sex of model animals, the female was chosen because researchers in reproductive biology were more familiar with the female reproductive

tract than the male organ. These researchers' choice of the female as the sex of future users of anti-fertility vaccines was supported by the government, the funding organizations and the pharmaceutical industry. Thus, the male as users of the vaccine has gradually disappeared. Based on these findings, van Kammen argues that the presumed sex of users of the technology was constructed by specific material and political factors, rather than exclusively determined by biological or cultural factors.

Timmermans and Leiter (2000) examine how thalidomide, the notorious drug which caused horrific disaster in the early 1960s, has reappeared as a life-saving drug for the treatment of leprosy, Erythema Nodosum Leprosum, and AIDS wasting syndrome in the US since the mid 1990s. A standardised drug distribution system, which was newly devised by a pharmaceutical company called Celgene and the Food and Drug Administration (FDA), played a key role in the transformation of the drug. By the 1990s, the advantage of thalidomide for the treatment of those diseases was known to patients, and its underground trade arose. The FDA called for the cooperation of the pharmaceutical companies and Celgene took it up. The distribution system that the company proposed and the FDA approved consisted of several elements: education of physicians, pharmacists and patients; contraceptive counselling; regimen of pregnancy testing; informed consent; managed distribution and mandatory outcomes registry survey. (Timmermans and Leiter 2000, 48) This system was constructed by not only the company but also other players, including physicians, pharmacists, patients, thalidomide victims, the FDA, and the drug itself. The jurisdictions and identities of the players were in turn redefined by the system. The risk of the drug has not disappeared but become more controllable and acceptable by the system of the standardisation of drug distribution.

These sociological studies of technological change in pharmaceuticals, together with sociological investigations of related issues such as biomedical laboratory life (Latour and Woolgar 1986), the genetics of cancer (Fujimura 1996) and the aetiology of peptic ulcer (Thagard 1999), provide us with detailed pictures of various aspects of biomedical research and development. They are obviously incompatible with "hard" technological determinism and most of them are not reconcilable with "hard"

social determinism. We can see how various human and non-human entities shape the biomedical science and technology in these works. However, these works do not necessarily show us the full process of drug discovery and development. The processes of clinical trials and regulatory examination have been well investigated. (Bodewitz, Buurma and de Vries 1987; Richards 1988; Abraham 1995; Epstein 1996) Marks (1997) describes in detail the history of clinical trials in the USA and the controversy over the randomised, controlled clinical trials. The processes of marketing and distribution of drugs and related instruments have also been examined but to the lesser extent. (Clarke and Montini 1993; Prout 1996; Timmermans and Leiter 2000) The process of biomedical research is described and studied in most detail. (E.g. Latour and Woolgar 1986; Fujimura 1996; Thagard 1999) However, amongst the literature mentioned above, only van Kammen (1999) examines both research process and development process, but her focus is relatively narrow: on the presumed sex of the future users. Therefore, the whole process of drug research and development has been little explored. This lack of a full picture is serious when we try to understand technological change in the pharmaceutical industry. In addition, most of these works tend to regard pharmaceutical companies as monolithic. Even worse, some regard the pharmaceutical industry as one unit of interest. However, as organisation studies indicate, private companies consist of heterogeneous entities. (Whipp and Clark 1986; Thomas 1994) A number of companies in the industry compete with each other by adopting different approaches. Most processes of drug research and development are conducted within pharmaceutical companies. We cannot fully understand the process of drug research and development without abandoning the monolithic view of pharmaceutical companies. Thus, we can now see what we want. It is a full, detailed study of the process of drug research and development. Both intra- and inter-organizational interactions should be examined. However, the examination of observable interaction is probably insufficient to understand technological change. We should take the historical and structural context into consideration. For this, international comparison may help.

2.3. Objectives and Research Design

2.3.1. Objectives

The main objective of this study is to answer the following question: Is it the case that the linear model of technological change can at least be applied to the pharmaceutical industry? If not, what is the process of technological change in this industry like? One of the main issues in technological change in the pharmaceutical industry is drug research and development, which includes research, pre-clinical tests, clinical trials, process development, application for regulatory approval and initial marketing activities. Although a lot of economic studies and organisation studies have investigated innovations in the pharmaceutical industry, the process of drug R&D has not been studied sufficiently in detail. Sociologists have revealed parts of the process of drug R&D, such as biomedical research, clinical trials and marketing activity, but the whole process including all these aspects has been little described sociologically. To answer our main research question, we should study the full, detailed R&D process in the pharmaceutical industry. As was seen in the literature reviewed in Sections 2.2.4.2 and 2.2.4.3, there are many actors inside and outside pharmaceutical companies involving in drug R&D. Therefore, we should examine both intra- and inter-firm activities. Furthermore, to understand the process, we should examine not only the interaction between relevant actors, but also the influence of historical and structural context, as the proponents of the social shaping of technology insist. (See Section 2.1.4) Thus, more specifically, we have the following questions. How are drugs discovered and developed? What kinds of interpretative flexibility exist in the process? How is the closure of interpretative flexibility achieved? What kinds of human actors are related to the process? What kinds of non-human factors are critical in the process? How do human and non-human actors interact with each other? How does transformation of the network of actors happen? Do structural and historical factors affect the process?

2.3.2. Research Strategy

To explore the process of drug R&D, I use case studies. A case study is a detailed investigation of a particular contemporary phenomenon with attention to its context by using multiple sources of evidence and various methods of data collection. (Robson 1993, p. 146; Yin 1994, pp. 12-13) One of the major strengths of the case study as a research method is its thickness, that is to say, richness in both the quantity and variety of information it includes. Because of the thickness, a case study provides us with a means of retaining "the holistic and meaningful characteristics of real-life events" (Yin 1994, p.3) The contextual thickness makes a case study appropriate for "how" and "why" research questions because answering these questions deals with operational links needing to be traced over time (Yin 1994, p.6).

Our main research objective is to understand the *process* of drug innovation, in particular that of drug R&D, rather than to analyse its results, for example, the relationship between specific organisational properties and R&D productivity. The meaningful interactions of various actors and entities, which cannot be specified in advance, should be captured. Most of our research questions belong to "how" questions. Therefore, case studies seem to be more appropriate for this study than survey and quantitative archival analysis. Because the control over events in real drug R&D is impossible and we do not know how to simulate it, this research cannot adopt an experimental approach. This study focuses on contemporary drug R&D. Interviews with relevant actors are possible and should be conducted. Taking these into consideration, I chose case studies as the research strategy of this research.

To obtain "analytic generalization" (Yin 1994, pp.30-32), I choose multiple case studies. By comparing different cases with different situational profiles, I try to clarify relevant actors and their specificity and generality. I compare different drug R&D processes in the same therapeutic area. I also compare drug R&D processes in different therapeutic areas. In addition, I compare drug R&D processes in two different countries, to understand in particular the influences of historical and

structural context. In these comparisons, I investigate what kinds of difference there are and how and why these differences arose.

2.3.3. Choice of Cases and Data Collection

I chose β-blockers and Ca antagonists (drugs for hypertension and other cardiovascular diseases), H_2 antagonists (anti-ulcer drugs), β-stimulants and inhaled steroids (anti-asthma drugs), LHRH analogues (anti-prostate cancer drugs), HMG-CoA reductase inhibitors (anti-cholesterol drugs), a cephalosporin antibiotic and an α_{1c}-blocker (a drug for urination disorder) as areas of case studies. They were chosen partly because they were new types of drug based on receptor and enzyme studies, which have been the main stream of drug R&D until very recently and partly because they were created by R&D in the pharmaceutical industry rather than in academic circumstances. These are essential because our interest is in modern drug innovation, which is mainly conducted by R&D in the industry. In addition, they were chosen partly because they have been extremely successful on the market and partly because they were properly "mature." They were discovered and developed in the period from the 1960s to the early 1990s. Most of them became the world or national top selling drug in each area. Although they are now mature products on the market, they are still widely used. The great success and maturity of these drugs also facilitated access to the information necessary for this research to cover the full process of R&D, partly because the relevant literature on such drugs is rich both in amount and in range, and partly because relevant people and companies feel easy to talk about their R&D process. Newer cases might have been more appropriate to provide insights into current and future drug R&D. In addition, newer cases might be less likely to be selective and glorified. However, if the cases were newer, it might be difficult to obtain a full picture of R&D process, and it would be much more difficult to gain access to relevant information because of the confidentiality surrounding pharmaceuticals R&D.

For the case studies, I used various published matters related to the cases, including academic articles, patents, textbooks, biographies, corporate histories, business

journal articles, newspaper articles, statistics, publications of companies, and those of industrial associations. From these, I obtained scientific, historical, chronological, causal and analytical information about the cases of drug shaping processes. I also conducted interviews with key researchers and staff related to the discovery and development of the drugs we examine here. I obtained causal information and situational information related to meaningful interactions between actors from interviews. Unfortunately, most internal documents related to cases were not available for reasons of confidentiality. Direct observation and participant observation were impossible because our cases are historical ones. Therefore, I mainly relied on the two sources of information: published materials and interviews. The quantity and quality of data used in each case study are not the same, mainly because of differences in the degree of publicity and confidentiality.

To select scientific papers, typically, I used review papers on the relevant drugs in medical journals, which I found in MEDLINE™. I also used textbooks in medicine, medicinal chemistry and pharmacology for this purpose. Then I collected papers written by the original researchers of each drug. Older papers were discovered from the references of these papers and interviewees. I also studied papers on the drugs written by other authors. Papers on results of clinical trials and different review papers were also studied. MEDLINE™ was fully used to search for these papers. I checked the references of these papers carefully and tried to cover often-cited papers. Key original researchers often wrote the story of drug discovery and development as journal articles or chapters of books. I used these writings as well. Some papers were offered by interviewees or companies. However, they were only a part of the literature used in each case study. I studied all these papers to reconstruct the process of drug R&D, and when I came across controversial issues, I sought further literature to understand the controversies fully.

Interviewees were selected by the author and/or relevant pharmaceutical companies. They include one or two key researchers of each drug except in the case of atenolol, other relevant researchers and development/marketing staff. The number of interviewees in each case study is: 4 in the cases of leuprorelin and cefotiam, 3 in the

cases of ranitidine and procaterol, 2 in the cases of mevastatin, salbutamol, BDP inhaler, salmeterol and fluticasone propionate, and 1 each in the case of propranolol, nicardipine, cimetidine, famotidine, goserelin and tamsulosin (in total 21 interviewees plus two anonymous interviewees related to Section 2.2.2). Key researchers were the project leaders of the relevant drug R&D and who might therefore be regarded as having detailed knowledge of the R&D process. Other interviewees were mainly chosen by companies as spokespersons of the development process of their drugs. Although there was little opportunity for the author to take part in the selection of such interviewees, these spokesperson-interviewees were also familiar with relevant drug development processes and greatly helpful. Each interview lasted for one to four hours, about two hours most commonly. Most interviews were individually conducted, but in a few cases, group interviews were conducted, for the convenience of companies. All interviews were tape-recorded and transcribed. The author also communicated with interviewees later by e-mail, fax or postal mail in order to obtain specific information related to the drug R&D process.

There was also an opportunity to choose which countries should be dealt with in the international comparison in this study. My choice here is Japan and the United Kingdom. There are two reasons. First, most of the literature on technological change in the pharmaceutical industry reviewed in the previous section deals with American cases. This may be due to the "fact" that a relatively small number of American companies virtually dominate recent innovation in pharmaceuticals. This may reflect greater interest in the pharmaceutical industry in the United States, may also be due to the fact that I look only at literature written in English. In any case, it is almost certainly true that both British and Japanese cases are much less investigated than the American cases. This makes research on the British and Japanese pharmaceutical industry interesting and useful.

Second, although Japanese products such as automobiles and electronics have often enjoyed competitive advantage in overseas markets, that does not seem to be the case in pharmaceuticals. (Howells and Neary 1995, p.1) Hawkins and Reich (1992) argue that Japanese pharmaceutical companies possess the potential to create innovative

products and have indeed created some world-class drugs, based on the analysis of Japanese-originated drugs in the US from 1960 to 1989. But, the overseas sales of 81 large- and medium-sized Japanese pharmaceutical companies contributed only 2.5% of their total sales in 1996. Even those of 20 leading Japanese companies accounted for only 7.2% of their total sales. (Japan Pharmaceutical Manufacturers Association 1997, I-21) Nevertheless, Japanese companies dominate the domestic market, which is the second largest single market for pharmaceuticals. Japanese companies accounted for about three quarters of Japanese pharmaceutical sales in 1996.[7] In contrast, the UK is one of the leading exporters of pharmaceuticals in the world. (Owen 1999, p.360) Exports amounted to 41% of gross output. (The Association of the British Pharmaceutical Industry 1997, p.13) Thus, the British pharmaceutical industry's performance in the world market is outstanding, though its machinery and electronics counterparts are only modestly successful. (Howells and Neary 1995, p.1) Several further contrasts between the British pharmaceutical industry and the Japanese pharmaceutical industry are reported. Firstly, British pharmaceutical companies have faced international competition since the late 1940s with the presence of American companies, but their Japanese counterparts were protected before the 1980s from international competition through the national health policy and industrial policy. Secondly, the British government has been close to the industry but has required world-class, innovative new drugs. By contrast, the Japanese government has not always been close to the industry but has approved even incrementally modified drugs. Thirdly, the British companies have focused on research but their Japanese counterparts have focused on marketing rather than research. (Howells and Neary 1995; Reich 1990; Owen 1999, pp.360-387) Finally, the linkage between public/academic research and the companies seems to be stronger in the UK than in Japan. (Hicks, Isard and Martin 1996) Because of these contrasts, the comparison between Japan and the UK is very interesting.

[7] The author's estimation based on Japanese Pharmaceutical Manufacturers Association (1997, I-5) and *Yakuji HandoBukku* (2000, p.97)

2.3.4. Data Analysis

For the understanding of the process of drug R&D, I reconstructed the cases by organising collected information historically and qualitatively. In order to reconstruct the process of drug R&D, written information and verbally obtained information were both used. The written stories of drug R&D were checked against the contents of interviews. The unwritten stories of drug R&D process, in particular the social aspect of the process, which is rarely conveyed in the scientific literature analysed, were obtained through interviews. On the other hand, the contents of interviews were also checked against and supplemented by the contents of relevant literature. I also tried to use the writings by authors other than interviewees when they were available in order to obtain more-balanced picture of the drug shaping processes. In this way, I tried to minimise the danger of misunderstanding due to my limited scientific expertises, the tendency toward the conventional realist explanation of drug R&D, the risk of lapses in interviewees' memories and the biases of interviewees' views.

Because my work was informed by theoretical perspectives in which innovation is seen as a process involved in heterogeneous human actors and non-human entities (see Section 2.1), it was essential in my data analysis to uncover the "social" as well as the "technical"[8] aspects of the shaping of drugs. First, therefore, when I was involved in the reconstruction of the drug shaping process, I paid attention to making it a detailed one including almost all relevant actors, factors and activities about which I had information. Second, I also paid attention to controversies, conflicts, competitions, collaborations, networking activities and other "social" interactions in the drug shaping process. Although they were rarely seen in most scientific papers, some papers included information on these "social" aspects of drug shaping. Interviews were particularly helpful in this regard. In addition, even if each paper did not talk much about "social" interactions, careful, comparative investigation into multiple papers sometimes revealed them. Third, during the reconstruction of the

[8] My findings support the claim of actor-network theory that innovation is intrinsically heterogeneous, and that technology is a seamless web (Hughes 1988) of "technical" and "social" actors and relations. These terms – "technical" and "social" – are therefore used here only as a shorthand convenience.

drug shaping process, I tried to understand each player's actions and the flows and causal relationships of events in as well-rounded a way as possible. When I did not understand something, I either asked interviewees or consulted further literature.

After I reconstructed each case of drug shaping, I compared different cases with others in the same therapeutic area, in different therapeutic areas, and in different social settings, i.e. the UK and Japan, to find similarities and differences. These comparisons helped me try to generalise my findings to some extent. On the basis of my preliminary data analysis, I also introduced several concepts including different aspects of drug shaping and different types of drug innovation, in order to contribute to the theorisation of the shaping of drugs and to understand the process better.

2.3.5. Reflexivity about Research Design

Although I believe that the case study is the most appropriate research strategy to improve our limited understanding of the *process* of drug innovation, there seems to be several alternatives in the way of data collection and analysis. First, the focus of research is on R&D rather than production and marketing. Although it would be better if the study included more information about production and marketing of each drug, I gave priority to R&D in the belief that it is the core of drug innovation and poorly understood so far. In any case, I do not ignore production and marketing because interests arising from these activities are reflected in the process of R&D. We can observe them when we examine the process carefully, as will be shown in case studies.

Second, the use of scientific papers in this study as one of the main sources of information might be taken as hampering a symmetrical, "relativist" treatment of scientific and technological knowledge because such papers usually incorporate a view of science as objective, cumulative and progressive.[9] Nonetheless, some of those papers explicitly suggest the existence of uncertainty and controversy in their

[9] On the relativist, symmetrical treatment of scientific and technological knowledge, see Bloor (1991), Collins and Yearley (1992) and MacKenzie (1996a, 9-18).

research areas. In such cases, I investigated a lot of literature in order to uncover uncertainty and controversy surrounding drug R&D, as will be shown in the cases of the risk of regular use of β-stimulants (Chapter 4), the role of histamine in gastric acid secretion (Chapter 5), the efficacy of LHRH analogues (Chapter 6) and the efficacy and safety of mevastatin (Chapter 7). Therefore, it seems wrong to say that the contents of scientific literature are completely incompatible with a relativist view of science and technology. If they are carefully examined, I believe, they can constitute useful evidence for relativist studies of science and technology. In this study, the uncertain and controversial aspects of drug R&D were also confirmed by and elaborated through the interviews.

Third, this research might be criticised for being a "great men" account, because it appears to be too dependent on interviews of key researchers. Interviews with other researchers must have countered this risk. However, it would have been extremely difficult to achieve this without the help of relevant pharmaceutical companies, which are very sensitive about confidentiality. Some companies were more cooperative than others in this respect, but even in such cases, I was unable to obtain many informants for a single case study. To minimise the potential biases and the lapses of memory of interviewees, therefore, I checked the contents of interviews with relevant literature as much as possible. Nevertheless, I think that there still remains room for a richer account in which the complexity of innovation process is better represented. If broader and deeper investigation into the cases had been possible, richer accounts, very likely giving greater weight to the roles of those other than R&D project leaders, would no doubt have emerged. However, I believe that this potential bias is not significant enough to undermine the major findings of this study.

Based on the research objectives and research design described above, we examine several cases of drug research and development in the same therapeutic area, including at least one British case and one Japanese case, in each of the following chapters up to Chapter 6. The next chapter deals with the cases of cardiovascular drugs.

Chapter 3: Cardiovascular Drugs

3.1. Introduction

In this chapter, we will see three cases of drug discovery and development in the cardiovascular area. Two of them, propranolol and atenolol discovered by ICI in Britain, are what are called beta-adrenergic receptor antagonists, commonly known as β-blockers. The third one, nicardipine discovered by Yamanouchi Co. Ltd. in Japan, is a drug classified as a calcium antagonist. Propranolol (Inderal®) was discovered in 1962, eventually became the first practically used beta-blocker and is still widely used. Atenolol (Tenormin®), which was discovered in the early 1970s, is the successor of propranolol and the best selling beta-blocker in the world. Nicardipine (Perdipine®) was discovered in 1971 and is one of the most frequently prescribed calcium antagonists in Japan. Of the four categories of anti-hypertension drugs, namely, diuretics, beta-blockers, ACE (angiotensin-converting enzyme) inhibitors and calcium antagonists, β-blockers are the most frequently used group of drugs in Britain, whereas calcium antagonists are most often used in Japan. (*Scrip Yearbook* 1991, p.63)

3.2. Propranolol

3.2.1. Introduction

The first beta-blocker that was investigated clinically was pronethalol. Pronethalol was discovered by (Sir) James Black and John Stephenson of ICI in 1960. Although it showed efficacy for the treatment of angina pectoris in clinical trials, it was replaced by propranolol partly because of its toxicity. Propranolol was discovered by Black's team in 1962. It showed about ten times higher potency than pronethalol and no serious side effects. Its clinical trials started in 1964 and it was marketed in 1965 under the trademark of Inderal. It was developed for the treatment of angina and arrhythmias at first, but later its usefulness as an anti-hypertension drug was also

found. It was highly successful in the market, and many pharmaceutical companies including ICI itself rushed into syntheses of its analogues.

Table 3.1: Major Events Related to the Discovery and Development of Propranolol

Year	Events
1958	Research project on beta-blocker started at ICI
1960	Synthesis of pronethalol
1962	Clinical trials of pronethalol Synthesis of propranolol
1963	Launch of pronethalol under restriction Clinical trials of propranolol
1965	Launch of propranolol

3.2.2. Discovery of β-Blockers

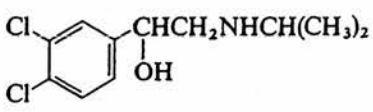
At a symposium on the history and the future of beta-blockade in Amsterdam in September 1975, James Black stated that his discovery of beta-blockers was based on the adrenergic receptor theory of R. P. Ahlquist and the discovery of DCI (dichloroisoproterenol) by researchers of Eli Lilly, an American pharmaceutical company. (Black 1976) Ahlquist examined responses of various organs to several sympathomimetic amines, which mimic the actions of noradrenalin (which is released from the sympathetic system and causes stimulatory or inhibitory responses of various organs). He found that there were two different orders of activity of the amines on various organs and suggested that there were two distinct types of adrenergic receptors, namely, the alpha and beta-receptors. (Ahlquist 1948) This theory however had been almost ignored until the discovery of DCI. (Black 1976) Ahlquist himself later in 1973 described the adverse circumstances when he published the paper:

> The original paper was rejected by *the Journal of Pharmacology and Experimental Therapeutics*, was a loser in the Abel Award competition, and finally was published in the *American Journal of Physiology* due to my personal friendship with a great physiologist, W. F. Hamilton. Bursting into print in 1948, it was ignored for more than 5 years except when someone referred to the methods used or the result obtained, but never to the concept. The reasons for this are obvious today: the concept did not fit with ideas developed since the 1890s on the actions of epinephrine. (Ahlquist 1973, 121)

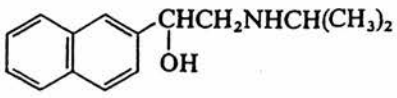
Black offered a more detailed explanation. According to him, Ahlquist's concept "can be seen to have been hidden in the long shadows cast by two giants---H. H. Dale, in England and W. B. Cannon, in the USA." (Black 1976, 11) Dale, who intensely investigated the activities of sympathomimetic amines on the body in the early 1900s, came close to Ahlquist's receptor idea. He wrote with G. Berger in 1910: "[t]here must evidently be something in those cells, or connected with them and them only, which has a strong affinity for these amines."(Barger and Dale 1910, 55) However, in the same paper, they also commented that the theory of receptive side-chains was very difficult to apply to their results because of the lack of common chemical characteristics among examined amines that plausibly explained the different affinity to specific site of tissue where specific receptive side-chains were assumed to exist. (Barger and Dale 1910, 56-57)[1] According to Black, Dale never referred to receptors again in his writing and never gave receptor theory the benefit of his huge scientific support. Because Dale was one of the most influential figures of his time, his neglect of receptor theory functioned as a strong negative signal from scientific orthodoxy.

[1] Receptors are not simple side-chains as Dale thought, but protein molecules and are flexible enough to bind many different substances. Therefore, agonists and antagonists exist. See, for example, Patrick (1995, pp.45-67).

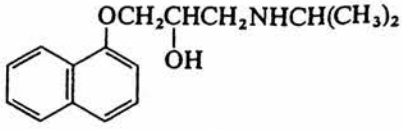
Figure 3.1: Various β-Blockers Discussed in This Chapter



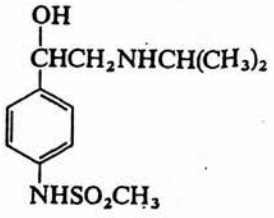
Dichloroisoprenaline



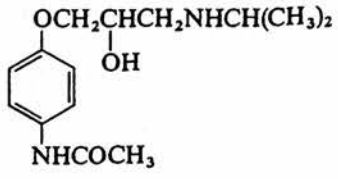
Pronethalol



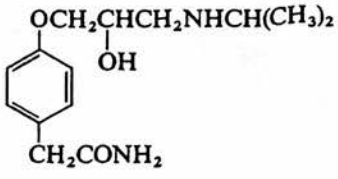
Propranolol



Sotalol



Practolol



Atenolol

Another and equally strong negative sign against receptor theory was an alternative explanation offered by Cannon. In 1933, he and A. Rosenblueth suggested new hypothetical substances: sympathin E and sympathin I. Black explained their idea plainly: a transmitter substance A was released at sympathetic nerve endings, and A then combined with either excitatory E or inhibitory I substances in the tissues to form complexes AE or AI (sympathin E and sympathin I). (Black 1976, 12) They elaborately explained the excitatory and inhibitory actions of sympathomimetic amines without using the concept of different receptors. It worked like the phlogiston theory. (Kuhn 1970) Thus, Black wrote: "the contemporary combined forces of a theory of multiple transmitters and a low regard for receptor theory as a basis for classifying drug actions were too much for the new hypothesis to overcome on the first round." (Black 1976, 12)

Then came the discovery of DCI. When a group of researchers at Lilly Research Laboratories of Eli Lilly, in Indianapolis in the US, discovered the compound, they were not looking for an adrenergic receptor antagonist but for a long-acting bronchodilator compound. (Maxwell and Eckhardt 1990, pp.6-7; Sneader 1985, pp.111-112; Shanks 1984) They synthesized a series of analogues of isoprenaline, a bronchodilator, and assayed them. They found that one of the compounds, DCI, blocked selectively some of effects of adrenaline and isoprenaline. They suggested that DCI was combining with certain "adrenergic inhibitory receptor sites" without itself causing much physiological effect, and yet was competing for these sites with physiologically active amines (Powell and Slater 1958, 488), such as adrenaline and isoprenaline. They reported their discovery at a scientific meeting in 1957. Neil Moran at Emory University in Atlanta, Georgia, became interested in the report and asked Eli Lilly for a sample of DCI. (Sneader 1985, p.112; Shanks 1984) He and M. E. Perkins tested it immediately and confirmed that DCI antagonized the changes in heart rate and muscle tension produced by adrenaline in 1957. They also found that DCI blocked the cardiac responses to adrenergic stimuli after the initial increase in heart rate, which indicated its partial adrenergic agonist activity. What was very important was that they linked this phenomenon with the Ahlquist's receptor theory. These results were published in 1958. (Moran and Perkins 1958) However, at that

stage, they had not yet labelled DCI a "beta-adrenergic blocking agent" as they did later in 1961. Neither did Eli Lilly fully seem to notice the value of their discovery of DCI at that time. According to Black, this was also related to the dominant idea at the time, mainly developed by Walter Cannon. Cannon developed the idea of homeostasis. He thought that the function of the sympathetic nervous system was the mediation of the "fight, fright and flight" reaction, that is to say, the sympathetic nervous system was working for survival. (Black interview; Black 1976)[2] For the people who believed the idea, it was not very wise to think about blocking the action of sympathetic nervous system.

It was Black who clearly saw the values of the Ahlquist's theory, the discovery of DCI and the initial combination of these two events by Moran and Perkins. He had been a senior lecturer of physiology at the Veterinary School of the University of Glasgow since 1950 until he joined the ICI Pharmaceutical's laboratory at Alderley Park in Cheshire in July 1958. (Kennedy 1993, p.130) During this period he had been interested in the treatment of angina pectoris. At the time, angina was treated by the strategy of increasing the supply of oxygen. (Black interview; Shanks 1984) Though there were surgical ways of doing this, pharmacologists started with nitro-glycerine, which was and has been widely used to treat angina. Nitro-glycerine dilates blood vessels, which was believed at that time to help the increase of the supply of oxygen to the heart. (Sneader 1985, p.142) Many attempts were made to find a new vasodilator drug that was specific for the coronary artery, but they were not fruitful.

Black came to examine another approach. When he worked with George Smith, a vascular surgeon in Glasgow, he saw Smith's experiment with dogs to increase the small amount of oxygen in the plasma to stop ventricular fibrillation. Black raised a question: "if a small increase of oxygen works, would the small decrease in the need of the heart for oxygen do the same thing?" He then directed his attention at the heart rate and sympathetic nervous system. His knowledge in clinical medicine helped there. On the one hand, he knew that not only exercise but also stress caused pain to patients with angina. On the other hand, he also knew from observations of surgical

[2] This interview with Sir James Black was conducted on 3rd March 1999

operations that stopping the heart beating faster would relieve angina. Thus, he wondered if it was possible to decrease the need of the heart for oxygen by slowing down the heart rate, which was known to be controlled by the sympathetic nervous system. He put it: "could one make the heart go a bit more slowly by stopping the activity in the sympathetic nervous system?" Thus, he began to look at adrenaline and came across Ahlquist's theory of the two types of adrenergic receptors in a textbook of pharmacology.[3] Although neither endocrinologists nor physiologists made much use of the concept of receptors at that time because of the reasons stated above, pharmacologists used the concept because it could explain beautifully the relationship between the concentration of a drug and its effectiveness on the body. He came to realize that what he wanted was a beta-adrenergic receptor antagonist. (Black interview)

In 1958, Black moved to the ICI Pharmaceutical's laboratories at Alderley. ICI had established all its pharmaceutical business in a separate division at the new site in 1957 to strengthen the business, especially, in the cardiovascular drug area. Garnet Davey, the then Head of Biological Research of the new Pharmaceutical Division of ICI, had learned of Black's interests and offered him a job. (Kennedy 1993, p. 130) Before long Black came upon the discovery of DCI and Moran's report on it. (Black interview; Black personal communication, January 2000; Kennedy 1993, pp. 130-131) In January 1959, he proposed a new project, saying: "the search for compounds which will block cardiac sympathetic responses constitutes a clear-cut pharmacological problem." (Shanks 1984) He and his colleagues made their own sample of DCI and tested it on the heart. They saw that the compound stimulated the heart rate, which meant that it would not work for the treatment of angina. However, it otherwise worked as a beta-adrenergic receptor antagonist. He decided to search for beta-adrenergic receptor antagonists devoid of the heart-rate-stimulating effect.

In February 1960, John Stephenson, a chemist at Alderley Park, synthesized a new compound, by replacing the two chlorine atoms in DCI with another phenyl ring.

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[3] Ahlquist wrote the chapter on adrenergic drugs in *Drill's Pharmacology in Medicine* published in 1954 from McGraw-Hill, which Black read.

(Sneader 1985, p.112; Shanks 1984, p.131; British Patent No. 909357) Black found that "the compound blocks the cardiac rate of tension changes produced by catecholamines, but differs from DCI in being free from intrinsic sympathomimetic [agonist] activity," (Black and Stephenson 1962, 314) in other words, that the compound was an effective antagonist of beta adrenergic receptors. The compound was named pronethalol (or nethalide, Alderlin®). It was subsequently tested on humans by A.C. Dornhorst and B.F. Robinson at St. George Hospital, London. In 1962, they confirmed that the drug blocked the cardiac action of catecholamines effectively in man and that exercise tolerance was increased in patients with angina pectoris by the drug. (Dornhorst and Robinson 1962) Furthermore, the full-scale clinical trials of pronethalol showed that the drug was effective for angina (Alleyne, et al. 1963), arrhythmias (Stock and Dale 1963), and hypertension (Prichard 1964). However, frequent occurrences of minor side effects of the drug were reported. (Alleyne, et al. 1963) Moreover, long-term toxicity tests revealed that the drug could cause cancer of the thymus gland in mice. (Paget 1963; Shanks 1984; Sneader 1985, p.112)[4] The British Government and British people in general became very sensitive about the safety of drugs after the revelation of the thalidomide disaster in 1962. The toxicological problem of pronethalol, therefore, was a major setback for the marketing of the drug. Eventually, the drug was marketed in the UK in November 1963, but under a restricted license. (Shanks 1984)

Meanwhile, Black did not stop searching for a better beta-blocker, because he was not convinced that he had obtained the ideal drug in pronethalol. He put it thus:

> The first one was what is called a prototype. And a prototype is just good enough. So, out of the principle, these studies in man showed in principle this thing would work. But it had many problems with it. One was that a quite number of patients got their bad dreams and also it was then found to be a carcinogen in mice. But, we didn't wait. We were trying to get something, which should be more potent and more selective and less toxic. We kept going. (Interview)

Elsewhere, Black stated: "I don't think there were any pressures to market

[4] According to Sir James Black, no one has ever repeated this observation. (Personal communication, January 2000)

pronethalol as a drug, rather than use it as a stepping-stone or probe, but if there were, Garnet [Garnet Davey, the research director] kept them away from me." (Kennedy 1993, p. 132)

After a large number of compounds were made (Black et al. 1964), Leslie Smith and Albert Crowther, chemists at Alderley Park, at last synthesized an analogue of pronethalol in 1962 (British Patent No. 994918; Shanks 1984), which was later shown to be about ten times as potent as pronethalol, with less side-effects, and not to be a carcinogen, by Black and his colleagues. (Black et al. 1964) The compound was named propranolol (Inderal®). Shortly after the synthesis of propranolol, the pronethalol's carcinogenic effect in mice was first reported in December 1962 (Shanks 1984), and the weight of R&D efforts rapidly shifted from pronethalol to propranolol. The first pharmacological and toxicological report of propranolol by Black and his colleagues was published in May 1964 (Black et al. 1964), and the clinical trials of the drug commenced in the summer of the same year, which soon indicated that propranolol was a safe and effective drug for the treatment of angina pectoris, hypertension and cardiac arrhythmias with a low incidence of side-effects. (Srivastava, Dewar and Newell 1964; Gilliam and Prichard 1965; Rowlands, Howitt and Markman 1965; Sloman, Robinson and McLean 1965; Various papers in the *American Journal of Cardiology*, Volume 18, Number 3, September 1966; Shanks 1984) The drug became the first beta-adrenergic receptor antagonist on the market when launched in July 1965. It took only two years and eight months from the first experiment of propranolol in an animal to its market launch. (Shanks 1984) It is obvious that the experience in pronethalol shortened the time for propranolol to clear the required criteria for the approval. Pronethalol was withdrawn from the UK market in October of the same year. (Shanks 1984) Then, on 10th and 11th November 1965, a major symposium entitled "Symposium on Beta Adrenergic Receptor Blockade" was held in Buxton, England, with sponsorship from ICI. (Braunwald 1966) The success of propranolol aroused rival companies to the search for a better analogue of the drug. (Sneader 1985, p. 113)[5] ICI also continued the research on β-

[5] Consequently, the market of beta-blockers got into the situation described as an "overcrowded field" by 1975. See the Lancet, April 26, 1975, 961-962. Another factor that promoted the rush of research into the area was the relative simplicity of the synthesis of an agent that has a good

blockers without interruption. (Howe et al. 1968; Crowther and Smith 1968; Howe and Rao 1968; Howe et al. 1969; Crowther et al. 1969; Howe 1969; Dunlop and Shanks 1968) Black left ICI in the middle of 1964. He put it thus:

> When a company has made a discovery of a new compound, what they want the scientists to do is to help them to promote the drug. So [ICI] wanted me to go to meetings and give papers... And they did not want me to stop working on beta-blockers. I wasn't interested in marketing. And I got interested in [histamine receptor antagonist], so I said I wanted to do this, and they didn't want me to do. So, I said, "all right. I'll go." (Interview)

Later, it was learned that propranolol had previously been synthesized by H. Koppe of C.H. Boehringer and Company, Ingelheim, shortly before pronethalol had been discovered. However, the company did not recognize the clinical potential of the compound, and no patent was claimed at that time. (Sneader 1985, p.113; Shanks 1984) Black recognized the value of the compound, and ICI took the patents related to it. Shanks wrote, "Black had made the crucial contribution to the discovery of β-adrenoceptor blocking drugs by realizing that they might be of value in the treatment of cardiac diseases and instituted a research programme to develop acceptable drugs." (Shanks 1984) Other authors also wrote, "[t]he major contribution of Black was to appreciate the possible value of developing compounds to inhibit the sympathetic to the heart, and to then persuade, and then lead a team of scientists at ICI to translate the idea into reality."(Cruickshank and Prichard 1987, pp.2-3)

Propranolol was very successful in the market. The biggest share of its sale was due to its efficacy in the treatment of hypertension, though the original researchers did not expect this use. The anti-hypertension activity of beta-blockers was discovered by Brian Prichard, when he was testing pronethalol in hypertensive patients at University College Hospital Medical School, London, in 1963. (Prichard 1964) He and P.M.S. Gillam found that propranolol also had an anti-hypertensive action in man in 1964. (Prichard and Gillam 1964) However, the anti-hypertensive activity of propranolol was not accepted immediately. There were some negative results. Gillam and Prichard attributed these negative results to an inadequate dose of the drug. They

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chance of being a β-blocker. See Le Count (1982, p. 120).

suggested that confusion arose from the misconception following the observation that showed that a relatively low dose of a beta-adrenergic blocking drug would completely work for another application. (Gillam and Prichard 1976, 71-72) The use of propranolol for the treatment of hypertension was well established by the early 1970s (Morrelli 1973; Simpson 1974, 90; Fitzgerald 1982, 104; Beevers and MacGregor 1999, pp.159-160), though the mode of the anti-hypertensive action of β-blockers has not yet been completely understood. (Lewis 1976; Kaplan 1998, p. 206) β-blockers had been the second most popular anti-hypertensive drugs after diuretics until 1991 (Kaplan 1998, p. 189, p. 205), and propranolol had been the leading β-blocker until it was superseded by new generation of β-blockers such as atenolol. Garnet Davey, the then research director, stated that the discovery of the application for anti-hypertension was "absolute luck." (Kennedy 1993, p. 133) Hypertension became the largest single use for propranolol and has enormously increased its market. (Kennedy 1993, p. 133) Black modestly commented that "commercial success has nothing to do with the quality of the science. It's the fact that so many people suffer from high blood pressure that has led to the attention. If high blood pressure had been as uncommon as multiple sclerosis, there wouldn't have been the same amount of notice taken of it." (Kennedy 1993, p. 134) However, the discovery of propranolol supported the theory of receptors, promoted further research on it, and changed the treatment of hypertension, angina pectoris and arrhythmias. This is shown in current textbooks in various disciplines: pharmacology (E.g. Rang, Dale and Ritter 1995, p.24, pp.148-170, pp.286-291, p. 295, pp. 317-319, p.433), medicinal chemistry (E.g. Patrick 1995, pp. 94-5, pp. 102-3), physiology (E.g. Berne and Levy 1996, p.165), and hypertension treatment (E.g. Kaplan 1998, pp. 205-212, p.231, p.277).

3.3. Atenolol

3.3.1. Introduction

Atenolol is a cardio-selective β-blocker discovered and developed by ICI. It possesses the advantages both of propranolol and of practolol. Practolol was the first

cardio-selective β-blocker, also discovered and developed by ICI in the mid-1960s, but ICI withdrew it in 1975 after it was found to be toxic. Practolol was also less potent than propranolol. Atenolol is as potent as propranolol, as cardio-selective as practolol, without the side effects that were frequently observed in the use of propranolol and without the serious side effects seen in the use of practolol. Atenolol was launched in the market under the trademark of Tenormin in 1976, and became the best selling beta-blocker in the world in the 1980s and 1990s.

Table 3.2: Major Events Related to the Discovery and Development of Atenolol

Year	Events
1964	Synthesis of practolol
1965	Pre-clinical studies of practolol, Launch of propranolol
1966	Discovery of cardio-selectivity of practolol Clinical trials of practolol
1968	Synthesis of atenolol
1970	Launch of practolol Pre-clinical studies of atenolol
1975	Withdrawal of practolol
1976	Launch of atenolol

3.3.2. In Search of Selectivity: From Propranolol to Atenolol

As mentioned in Section 3.2.2, ICI continued research on beta-blockers without interruption after the discovery of propranolol. They synthesized and tested a number of analogues of propranolol and pronethalol. (E.g. Howe et al. 1968; Crowther and Smith 1968; Howe and Rao 1968; Howe et al. 1969; Crowther et al. 1969; Howe 1969) They also studied β-blockers synthesized by other companies. (Dunlop and Shanks 1968) Of these intensive and extensive studies on β-blockers at ICI, two sets of studies focused on a particular problem related to the local anaesthetic property of propranolol.

In 1965, Vaughan Williams reported that both propranolol and pronethalol are local anaesthetics. (Vaughan Williams 1966) This raised a question whether the beneficial effect of the drug in angina resulted from the beta-receptor blocking effect or a local anaesthetic effect. (Shanks 1984) Researchers at ICI resolved propranolol into two optical isomers and found that the (-)-isomer was shown to be 60-100 times more potent than the (+)-isomer in blocking beta-receptors, whereas both propranolol and its (+)-isomer were equally potent local anaesthetics but the (-)-isomer was less potent in local anaesthetic activity. (Howe and Shanks 1966; Shanks 1984) The researchers decided to begin studies with the D- (i.e. (+)-) isomer of propranolol to determine the contribution of local anaesthetic activity to the therapeutic effect of propranolol. (Shanks 1984)

Another approach taken by ICI to this problem was to develop a β-blocker that was not a local anaesthetic. (Shanks 1984) Besides propranolol, a β-blocker which was synthesized outside the company helped the researchers' thinking. The β-blocker was synthesized by A.A. Larcen at the Mead Johnson Pharmaceutical Company in October 1960, though the company was not searching for a β-blocker at that time. (Sneader 1985, p. 113; Shanks 1984) The compound was named sotalol, and, later, found to be a β-blocker. What was important was that sotalol was devoid of local anaesthetic activity. (Lish, Weikel and Dungan 1965; Shanks 1984) The compound was also devoid of side effects on the central nervous system due to its hydrophilic nature. Propranolol had this effect and could cause vivid dreams after taking it, which was one of major side effects of the drug. (Sneader 1985, p. 113; Simpson 1974) The ICI researchers synthesized sotalol and its derivatives, including its phenoxy derivative (ICI 50232) and the acetamido derivative of ICI 50232 (ICI 50172) in the summer of 1964. ICI 50172 was found to be a β-blocker without local anaesthetic activity like sotalol, though less potent in beta blocking than propranolol. ICI 50172 was named practolol, and ICI decided to develop it for clinical studies in which a comparison would be made between practolol and the D-isomer of propranolol to determine the role of blockade of beta-adrenergic receptors and of local anaesthetic activity in the effectiveness of propranolol in angina and

arrhythmias. (Shanks 1984)

The comparative studies between practolol and D-isomer of propranolol did not come to fruition because unique and more interesting pharmacological properties of practolol were unexpectedly discovered and research efforts were concentrated on understanding of these properties. During 1965 and 1966 detailed pharmacological studies were made in animals with practolol. In April 1966, Robin Shanks and his colleagues at ICI almost by accident discovered that practolol blocked beta-adrenergic receptors in the heart but not those in bronchial or vascular smooth muscle. (Dunlop and Shanks 1968) Practolol was described as a cardio-selective beta-adrenergic blocking drug. (Shanks 1976) This property was especially important because the biggest problem of propranolol was its lack of selectivity in its affinity of beta-adrenergic receptors. The beta-receptors are widely distributed in the body, and related not only to the heart but also to the bronchi and some other organs. The most serious problem is that beta-adrenergic receptor antagonists without the selectivity cause the constriction of the bronchi, which can be life-threatening in patients with asthma. This side effect was obvious in the use of propranolol, because it equally affected both the beta-receptors on the heart and those on the bronchi. (Rand, Dale and Ritter 1995, p.150, pp.166-167) Practolol blocked the beta-receptors on the heart selectively, and was almost devoid of this side effect.[6]

This phenomenon was explained by the hypothesis of Lands and his colleagues of Sterling-Winthrop Research Institute that there were two types of beta-adrenergic receptors: β_1 receptors mediating responses in the heart and β_2 receptors mediating responses in bronchial and vascular smooth muscle. (Lands et al. 1967) Practolol blocked those receptors that Lands had classified as β_1 and had little effect on β_2 receptors. In subsequent studies, practolol was shown to be cardio-selective in man (Brick et al. 1968), and was taken forward to clinical trials. The clinical trials confirmed that practolol did not block the bronchodilator action of isoprenaline and did not produce wheezing in asthmatic patients. (Powles, Shinebourne and Hamer 1969) An international conference on practolol was held on 5th and 6th June 1970 in

[6] Practolol was not absolutely devoid of this side effect. See the Lancet, April 26, 1975, 961-962.

London. (Lewis (ed.) 1971) Practolol (Eraldin®) was launched on the market in 1970. (Sneader 1985, p. 114)

Practolol, however, was withdrawn from general use in 1975, because it caused serious side effects (in the worst case, loss of eyesight) in a small number of patients who had taken it orally for a long time. (Shanks 1984; Sneader 1985, p.114; Editorial, *British Medical Journal*, 14 June 1975; Cruickshank and Prichard 1987, pp.835-839) The use of the drug was restricted to specialized hospital units after that. The drug that eventually took over the market of practolol in 1976 was ICI-66082 (atenolol), which had been synthesized by David Le Count in 1968, a year before the market launch of practolol. (Fitzgerald 1977; British Patent No. 1285038) This compound, therefore, was not searched for because of the withdrawal of practolol, but had already been discovered in the continuous research on β-blockers in ICI, in which the researchers had searched for a drug with both the advantages of propranolol and those of practolol.

Practolol had two obvious drawbacks, apart from the side effect mentioned above: it was less potent than propranolol on the heart and it also had a partial agonist activity. (Barrett 1971; Barrett 1977; Fitzgerald 1977; Le Count 1982, p. 124) These two drawbacks were the main targets of the research after the discovery of practolol because the long-term toxicity of practolol was not known when the research was conducted. (Wiseman 1971) Therefore, the demanded profiles of the next drug to practolol were to be as potent as propranolol on the heart and to be devoid of partial agonist activity, while it was also necessary for the drug to have less effect on the bronchial and vascular smooth muscle (i.e. cardio-selective) and to be free of local anaesthetic activity, like practolol. (Barrett 1977; Fitzgerald 1977; Le Count 1982, p. 119) In addition, it was required for the drug to be highly water soluble (hydrophilic) so as not to penetrate the central nervous system and cause side effects like vivid dreams. (Barrett 1977) To find a drug that satisfies these profiles was important not only for improving therapies of angina and hypertension but also for understanding the mode of action of β-blockers. All β-blockers available at that time had mixed activities: general β-blocking activity, cardio-selective β-blocking activity, local

anaesthetic activity and partial agonist activity (Table 3.3). Knowledge on the effects of each activity on the body was poor. Scientists in the industry wanted to know the contribution of each activity to the safety and efficacy of β-blockers. They strongly wanted a drug that had β-blocking activity only so that they could compare its effects with those of other β-blockers. (Fitzgerald 1977)

Table 3.3: Some Pharmacological Properties of β-Blockers

Drug	β-blocking potency	Cardio-selectivity	Local anaesthetic act.	Partial agonist activity
Available				
Propranolol	++	-	+	-
Sotalol	+	-	-	-
Oxprenolol	++	-	+	+
Practolol	+	+	-	+
Required				
Atenolol	++	+	-	-

(Sources) Fitzgerald (1977) and Heel et al. (1979), Partially edited by the author

The ICI research team at that time was led by Arthur M. Barrett, a pharmacologist, and included both pharmacologists and chemists. (Fitzgerald 1977) Both sorts of expert were required to change their approaches. The pharmacologists needed to modify biological screening procedures so that they could identify each activity of the examined compound. (Barrett 1977) A screening sequence with five stages was devised. (Le Count 1982, pp. 120-126) For the chemists, it was relatively easy to achieve potency as strong as propranolol, but it was not easy to achieve the other demanded profiles. This was because the structural features responsible for the presence or absence of the other properties were not obvious. First of all, in order to achieve cardio-selectivity, the unique structure of practolol was carefully studied. One of the chemists, Roy Hull, considered that the acidic nature of the proton in the unique structure of practolol, $-NHCOCH_3$, contributed to the cardio-selectivity. He

suggested an alternative side-chain to his colleague, Le Count. (Fitzgerald 1977; Barrett 1977) Because the original suggestion was difficult to synthesize, (Fitzgerald 1977) Le Count tried another side-chain, $-CH_2CONHR$,[7] at the same position as $-NHCOCH_3$ in practolol, based on Hull's hypothesis and his own thought that the NH chain could also play a crucial role. (Le Count 1982, p. 126) The parent compound, atenolol, was the one with H at the R position of the side-chain, $-CH_2CONHR$ (that is, $-CH_2CONH_2$), which was synthesized through a unique, but very convenient, method. (Le Count 1982, pp.126-127) Within two months of its synthesis in December 1968, the compound was found to be a cardio-selective β-blocker, as expected. To the researchers' surprise, however, it was found to be devoid of partial agonist activity and also devoid of local anaesthetic activity. (Le Count 1982, p. 126; Barrett et al. 1973; Fitzgerald 1977) Thus, the compound unexpectedly achieved all of the targets at the same time. A number of analogues of the compounds were also synthesized. (Le Count 1982, pp. 127-131) Many of them were cardio-selective β-blockers.[8] However, none was closer than atenolol to the initial target. Any additional modification led to the loss of one or more demanded profiles. For example, a modification that enhanced the potency reduced the hydrophilic property. (Le Count 1982, pp. 127-131) Several compounds based on other approaches were also compared with atenolol, but none satisfied all of the initial requirements. (Fitzgerald 1977)[9] Although atenolol was not an "ideal" β-blocker with cardio-specificity (i.e. active on the heart only), it was at least the closest to the "ideal." (Barrett 1977) In addition, it is said that atenolol was chosen particularly because it was believed to be the most potent one in anti-hypertension activity. (Fitzgerald 1982, 113-114; Bilski personal communication) As mentioned in the previous section,

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[7] R in molecular structures represents a generalised group of atoms, which are replaceable and to be examined with each other in order to obtain the best one. Typically, this includes hydrogen, methyl, ethyl and other alkyl groups.

[8] Ironically, a subsequent analysis with those related compounds showed that the Hull's hypothesis was not necessarily correct. See Barrett (1977).

[9] According Dr Andrew Bilski, an expert in ß-blockers at AstraZeneca (formerly ICI), there were three other candidates apart from atenolol, namely ICI 72222, ICI 78748 and ICI 89406. They had different advantages and disadvantages. For example, ICI 89406 was more cardioselective than atenolol. However, all but atenolol had partial agonist activity, which was thought to result in less anti-hypertension activity than atenolol. ICI 78748 had an activity to induce histamine release, which was another reason for not being chosen. (Personal communication, May 2000)

hypertension was the largest market for β-blockers. Thus, atenolol was chosen to be developed as a drug.

Clinical trials confirmed the efficacy of the drug for the treatment of hypertension and angina pectoris, its cardio-selectivity, and its lack of serious side effects, including the one that was reported in the long-term use of practolol. (Hoffbrand (ed.) 1977; Heel et al. 1979) Many of clinical trials included the comparison with propranolol. (E.g. Astrüm and Vallin 1974; Roy, Day and Sowton 1975; Singh et al. 1975) Atenolol was not more potent than propranolol but its cardio-selectivity, its absence of local anaesthetic activity, and its lack of partial agonist activity were regarded as advantages. An unexpected, additional advantage of the drug was that it was longer acting so that it could allow once a day dosage for the treatment of the hypertension. (Fitzgerald 1977; Heel et al. 1979) It is notable that the number of papers on clinical trials of atenolol was much larger than that of propranolol. Atenolol was launched in 1976 under the trademark of Tenormin. (Zeneca 1993 *Annual Report and Accounts*, p. 16) An international symposium on atenolol was held on 4th to 6th October 1976 in Nice, France. (Hoffbrand (ed.) 1977) Atenolol became one of the world's best-selling cardiovascular drugs in the 1980s. Even in 1991, 15 years after its launch, it was amongst the top 5 selling drugs in the world with the sales amounting to 1180 million dollars. (*Scrip Yearbook* 1993, p.47) The drug, in 1993, accounted for 25% of the sales of pharmaceutical products at Zeneca, which has been separated from ICI since 1993. (Zeneca 1993 *Annual Report and Accounts*, p. 15)

3.4. Nicardipine

3.4.1. Introduction

Nicardipine is one of the drugs called calcium antagonists. It was discovered and developed by Yamanouchi Co. Ltd. in Japan in the 1970s. When it was discovered, the researchers at Yamanouchi did not know its mechanism of action. However, because it showed remarkable potency in coronary and cerebral vasodilation, it was

chosen for development. During its clinical trials, the concept of calcium antagonism arose and provided an explanation for the action of the drug. Nicardipine was launched in the Japanese market under the trademark of Perdipine in 1981, and became one of the best selling cardiovascular drugs in Japan in the 1980s.

Table 3.4: Major Events Related to the Discovery and Development of Nicardipine

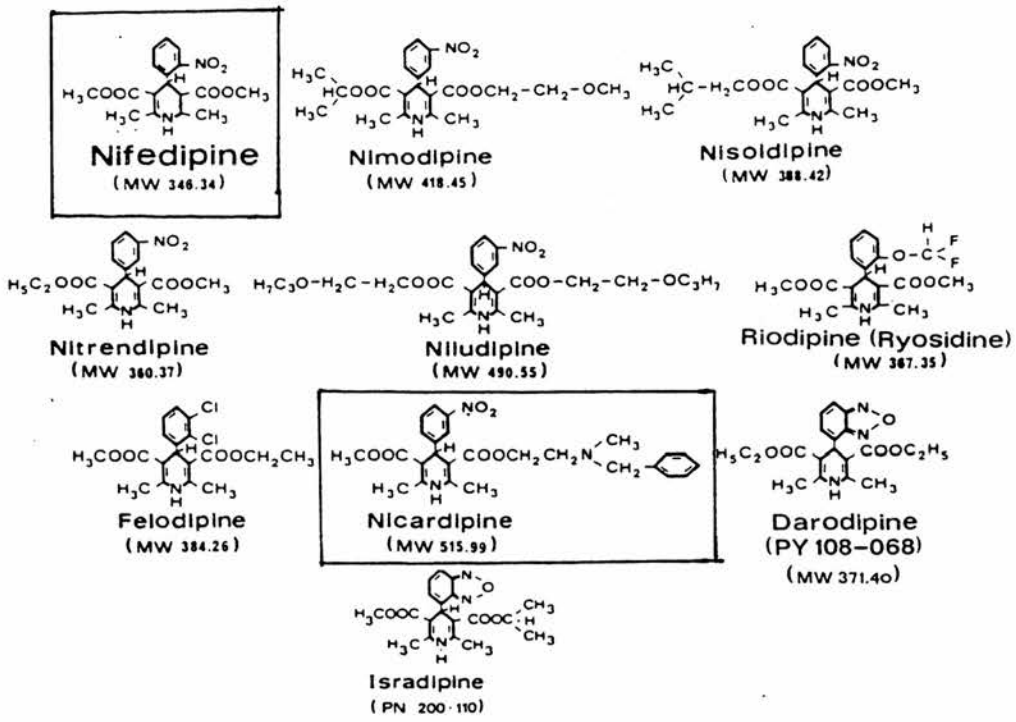
Year	Events
1966	Synthesis of nifedipine (patented in 1967)
1969	Clinical trials of nifedipine in Japan (in German in 1970) Finding of the calcium antagonist activity of nifedipine (published in 1972) Start of research on the analogues of nifedipine at Yamanouchi
1972	Discovery of nicardipine
1974	Clinical trials of nicardipine (cerebral vasodilator) [in Japan]
1976	Launch of nifedipine (anti-angina) [in Japan]
1977	Clinical trials of nicardipine (anti-hypertension) [in Japan]
1981	Launch of nicardipine (cerebral vasodilator) [in Japan]
1982	Extension of application of nicardipine (anti-hypertension) [in Japan]
1985	Extension of application of nifedipine (anti-hypertension) [in Japan] Suspension release tablet of nifedipine [in Japan]
1988	Suspension release tablet of nicardipine [in Japan]

3.4.2. Discovery and Development of a Calcium Antagonist in Japan

When Toichi Takenaka joined Yamanouchi Pharmaceutical after graduating from university in 1964, he was interested in the activities of vasodilators. However, vasodilators at that time were not highly rated as drugs for angina pectoris and hypertension, partly because existing vasodilators such as hydralazine, dipyridamole and cyclandelate were not very effective, and partly because the advent of β-blockers in the mid-1960s attracted most researchers' and physicians' attention to the new

type of drugs. Yamanouchi also went with the tide, and eventually discovered a β-blocker, indenolol, in 1968. Takenaka had to stop his research on vasodilators because he was involved in the research of the β-blocker. However, not long after he finished the work on the β-blocker, he came across a new series of compounds, 1,4-dihydropyridine derivatives. (Takenaka interview)[10]

Figure 3.2. Various Dihydropyridine-type Calcium Antagonists



(Source) Fleckenstein (1988)

[10] This interview with Dr Toichi Takenaka was conducted on 22nd January 1999.

The compounds, called 1,4-dihydropyridine derivatives, did not originate with Yamanouchi. Since the mid-1960s, an American company and a German company had been studying them. In the United States, Bernard Loev and his colleagues at SmithKline and French Laboratories were interested in 1,4-dihydropyridine derivatives, a simple synthesizing procedure of which had been discovered by A. Hantzsch in 1882, because the pharmacological properties of this category of compounds were not well-known even though dihydropyridines were involved in various biochemical processes. (Loev, Ehrreich and Tedeschi 1972; Loev and Snader 1965) They studied the derivatives and found that a compound had a long-lasting hypotensive activity in dogs when administered by injection. However, it did not work when given orally. They synthesized a large number of compounds to find an orally active compound. Eventually, they found one potent hypotensive compound (SKF 24260) that was active even by the oral route, and published it in 1972. (Loev, Ehrreich and Tedeschi 1972; Sneader 1985, pp. 143-144) They tried to develop the compound as a drug, but gave it up later because of its toxicity. (Takenaka interview)

In Germany, F. Bossert, a chemist at Bayer AG had been studying coronary dilating agents since 1948. He and W. Vater, a pharmacologist, found that 1,4-dihydropyridines possessed a strong coronary dilating activity. They synthesized and tested more than 2000 of its derivatives, and finally discovered a highly potent coronary vasodilator (BAY a 1040) in 1966. (Bayer (Japan) 1994; Bossert and Vater 1971) The compound was orally effective. They patented this and similar compounds in 1967 before the SKF team protected their work by patents. (Sneader 1985, p. 144) The clinical trials of the drug started, first in Japan in 1969, then in Germany in 1970, for the treatment of angina pectoris. This was because some Japanese medical experts had been interested in coronary dilating agents for the treatment of angina. The drug, named nifedipine (Adalat®), was approved in Japan as an anti-angina drug 1975, and launched in the market in 1976. In Germany, it was launched in 1975. (Bayer (Japan) 1994; *Gekkan Mikusu*, Volume 24, No.14, December 1996, p. 62) Meanwhile, Albrecht Fleckenstein at the University of Freiburg had been studying the mechanism of the vasodilating activity of nifedipine since 1969. He found that

the drug was a strong calcium-ion-channel blocking agent (in short, a Ca antagonist) and published his results in 1972. (Fleckenstein et al. 1972; Fleckenstein 1977; Fleckenstein 1988) Vascular muscle cells contract when the intracellular calcium concentration rises. The entry of Ca^{++} into cells is regulated by calcium-ion-channels on the cell membrane. Therefore, by blocking the entry of Ca^{++} into vascular muscle cells, we can stop vasoconstriction. Fleckenstein had elaborated the concept of Ca antagonists since 1963, and nifedipine contributed to establishing the concept. He wrote in 1988:

> No doubt, the discovery of the top Ca^{++} antagonist nifedipine marked the definite breakthrough of the concept of Ca^{++} antagonism and induced enormous efforts by the pharmaceutical industry to expand the new Ca^{++} antagonistic drug family by further syntheses. (Fleckenstein 1988, 6)

In the late 1960s, Yamanouchi licensed three vasodilators from an overseas company, though they were not 1,4-dihydropyridine derivatives. In order to test the properties of these compounds, they had to learn the methods of biological tests on vasodilators, because the company, which had started its own research for new drugs in 1963, did not have sufficient skills. They learned the related techniques of experiments by sending their researchers to domestic universities. Using the compounds and the techniques, they obtained methods of assay for vasodilators. Although none of the compounds turned out to be a promising drug, the technology obtained through this experience contributed to their later work. (Takenaka interview)

Masaru Iwanami and his fellow chemists at Yamanouchi started pharmacological studies on 1,4-dihydropiridine derivatives in order to discover a vasodilator in 1969. (Yamanouchi 1994) They learned about the substances from information found by a team of literature and patent investigators in the company. The original sources in this case were the patents of Bayer and SmithKline. They synthesized a number of the analogues. Takenaka, who had at that time been conducting the biological screening of hundreds of compounds to find a potent vasodilator, tested these 1,4-dihydropiridine derivatives as well. He found that one of them showed a remarkable potency he had rarely seen before. He put it: "I didn't know the concept of calcium antagonists at that time. But, I observed the reactions of animals given the compound,

and strongly felt that this was very much different from the existing vasodilators." Takenaka, Iwanami and their colleagues decided to keep examining the compound and its analogues. (Takenaka interview)

Although the compound was highly potent, it was less soluble in water than Bayer's 1040 or SKF 24260. This meant the compound would not work when given orally. Therefore, the efforts of the Yamanouchi chemist team were directed to finding more water-soluble analogues. Many approaches to getting a high water-solubility reduced the potency of the compound. The productivity of reactions was also important. After an enormous effort, they got a few candidates to develop as a drug. There was a trade-off between water-solubility and potency. They selected one of the most active compounds in their study though it had a relatively low water-solubility. Nevertheless, even the selected compound (YC-93) had very high water-solubility compared to existing alternatives: it was more than 100 times higher than that of Bayer's 1040 or SKF 24260. (Iwanami et al. 1979) The selection was made in view of the potency, bioavailability (i.e. water-solubility), duration and uniqueness of the compound. (Iwanami et al. 1979; Takenaka interview) YC-93 was discovered in 1972 (Takenaka interview) and patented in 1974. (Iwanami et al. 1979; Japanese Patent No. 109384; Belgian Patent No. 811324)

In pre-clinical tests with animals, YC-93 was found to be a potent cerebral and coronary vasodilator with low toxicity. Takenaka and his colleagues also confirmed that it was well absorbed by the oral route. (Takenaka 1974; Takenaka et al. 1976) They seemed, however, not yet to notice that the drug had a calcium antagonistic activity. In the paper published in 1976, they only mentioned: "The coronary vasodilator mechanism of YC-93 seemed to be different from that of dipyridamole." Later, they learned the concept of calcium antagonism from the literature and used the concept effectively to persuade medical doctors to conduct clinical trials of the drug. (Takenaka interview)

Takenaka and his colleagues decided to propose the development of the compound. Since the company had only recently started its own research for new drugs, it did

not have a systematic procedure to evaluate a drug development project when YC-93 was discussed.[11] Masuo Murakami, the then director of the central laboratory of the company and who had been a professor at the Research Institute of Industrial Sciences, Osaka University before joining the company, had absolute discretion on research policy and management. Researchers at Yamanouchi used to propose their projects directly to him, and he decided whether to take or to drop their proposals. Takenaka put it thus:

> At the time, we used to ask the director to let us do this research, and he used to say, "OK, go ahead." We were in such atmosphere. Research management wasn't strict. We did what we wanted to do, and when we got good results on it, we would propose its development. We enjoyed an extremely high freedom about research. Later, when [famotidine] was developed, the atmosphere was less free and there was a formal procedure of project proposal. But, in [YC-93, nicardipine] case, we didn't have such procedure. I briefly explained the results to the director in a research meeting and asked, "I've got such a good compound. Let me do this." (Interview)

Murakami immediately gave Takenaka an OK. Although Takenaka succeeded in obtaining an organisational authorisation in this way, he heard some voices of anxiety from the marketing side. They were anxious about the resistance of medical doctors whom they asked to conduct clinical trials of the drug. Only several years before, in 1967, a modern approval system for new drugs was introduced in Japan, and this drug was the first one Yamanouchi sought to develop under this new regulatory system. In fact, some doctors doubted the clinical value of vasodilators. Yamanouchi's representatives and researchers faced a lot of difficulty in obtaining such doctors' cooperation. They were trying to persuade doctors with data from animal experiments, but it was not very easy.

Just in time, they learned of the concept of calcium antagonists from the literature on nifedipine (Takenaka interview), which I mentioned above. Because of the similarity between the structure of nifedipine and that of YC-93, it was obvious that the mechanism of action of YC-93 could also be explained by calcium antagonism. At

[11] Costs, rather than estimated sales, were the only economic factor that was taken into consideration about R&D in the company at that time. (Takenaka interview)

that time, nifedipine was also in its clinical trials in Japan. Furthermore, another drug with a different chemical structure from 1,4-dihydropyridines, diltiazem, which had been serendipitously discovered by researchers at Tanabe Pharmaceutical in the mid-1960s and was also undergoing clinical trials at the time, was found to be a calcium antagonist as well. (Nakajima et al. 1975; Tanabe 1994; Fleckenstein 1977; Fleckenstein 1988) That is to say, three potent vasodilators were clinically tested in Japan at the almost same time, in the 1970s, and during their clinical trials it became clear that all of them were calcium antagonists, a group of drugs whose mode of action was newly explained. This new concept attracted doctors, especially leading doctors at universities. (Takenaka interview) Yamanouchi, the latecomer of the three, was able to enjoy the benefit of the popularity of the concept of calcium antagonism in academic physicians. As Takenaka put it, "Voices from outside are very important in Japan. What opinion leaders say is crucial. ... In Japan, especially at that time, people didn't trust any Japanese work until someone else announced it's OK." (Interview) Probably, for leading academic physicians in Japan, Fleckenstein was "someone else," whereas for other physicians, the leading academic doctors were the "someone else." However, it might be worthwhile noting that people at that time did not know whether calcium antagonists would work practically even though they had obtained the concept. People were beginning to recognize calcium antagonism as a new approach to the treatment of hypertension, but the clinical value of calcium antagonists was far from established. Although many aspects of calcium antagonism were still uncertain, the concept helped Yamanouchi's representatives persuade doctors. Yamanouchi was able to start clinical trials of YC-93 in 1974.

The clinical trials of YC-93 started first as a cerebral vasodilator. There were two reasons Yamanouchi chose this application rather than a coronary vasodilator. On the one hand, specialists in coronary medicines at that time were doubtful about the effectiveness of coronary vasodilators for the treatment of angina, because it was known that the then existing vasodilators like dipyridamole dilated only the healthy coronary artery and that this might worsen the shortage of blood supply to the diseased coronary artery (the "coronary steal" phenomenon). Calcium antagonists increase blood supply to both healthy and diseased coronary arteries, but at that time

it was not possible separately to measure each blood flow to show this. As to cerebrovascular disorders, however, it was known that the total blood supply was related to patients' conditions. On the other hand, the number of patients with cerebrovascular disorders in Japan was higher than that of patients with angina at that time. It would have taken more time and cost more to have conducted clinical trials of the drug for the treatment of angina. (Takenaka personal communication, December 1999)

In 1975, the drug progressed into Phase II, in which it was given to patients with blood-flow disorder in the brain. Then, it experienced Phase III, double-blind tests with an existing drug. Yamanouchi cleared clinical trials and applied for the approval of manufacturing of the drug in 1979. The drug, named nicardipine, was approved in 1981. It was launched in the market under the trademark of Perdipine in the same year. (Yamanouchi 1994; Takenaka interview)

Meanwhile, the clinical trials of YC-93 as an anti-hypertensive drug also started in 1977. This was partly because its anti-hypertensive activity was confirmed in the course of its clinical trials as a cerebral vasodilator. (Yamanouchi 1994)[12] However, there was another reason why the clinical trials as an anti-hypertensive drug came late: the anticipated official price of YC-93 as a cerebral vasodilator was higher than as an anti-hypertensive drug. (Takenaka interview) That is to say, this choice of application was made not only from a medical point of view but also from an economic point of view. Of course, Yamanouchi did not give up the huge and growing anti-hypertension market. After clearing another set of the clinical trials of nicardipine for the treatment of hypertension, and after the drug was approved as a cerebral vasodilator, Yamanouchi applied for approval of the extension of nicardipine's application. This extension of application was approved in 1982, and nicardipine became the first calcium antagonist approved for the treatment of anti-hypertension. (Yamanouchi 1994) Although nifedipine had been approved as an anti-angina drug in 1975, it was not until 1985 that the drug became in Japan available for

[12] The efficacy of calcium antagonists for the treatment of hypertension was established in the 1980s. See Kaplan (1998), p.216.

the treatment of hypertension. (Bayer (Japan) 1994)

The dose of nicardipine tablets was originally three times daily. Later, the suspended release tablet (twice daily) of the drug was developed especially for the treatment of hypertension. This was approved in 1988. The injection formula for its use during a surgical operation was also developed and approved in 1988; its water-solubility made injection possible. Nicardipine was also launched in other countries, including the United States, France, Italy and the United Kingdom in collaboration with American and European companies. (Yamanouchi 1994) However, in these countries, the applications of this drug are anti-angina and anti-hypertension like nifedipine, rather than cerebral vasodilatation. (*British National Formulary*, 35, March 1998, p.99; Bowles et al. 1981; Gelman et al. 1983; Iliopoulou, Turner and Warrington 1983; Lambert et al. 1985; Kathleen et al. 1986)

Nicardipine was very successful in the Japanese pharmaceutical market. Annual sales in the 1980s and early 1990s were about 40 billion yen (about 200 million pounds if one pound equals 200 yen). It was among the top 5 selling drugs in Japan from 1986 to 1990. Three years after nifedipine was approved for anti-hypertensive use and its suspended release tablets were launched in 1985, sales of nicardipine in Japan were surpassed by those of nifedipine. (*Gekkan Mikusu*, Volume 24, No.14, December 1996, p. 41) In 1996, the estimated sales of nicardipine and nifedipine were 24 billion yen and 38 billion yen respectively, whereas that of atenolol, the top selling beta-blocker even in Japan, was 11 billion yen. (*Yakuji Handobukku* 1997, p.268) The official prices of nifedipine, nicardipine, propranolol and atenolol per day in 1994 were 666~1220, 626~1200, 619 ~1436, 1290 yen respectively. (*Yakka Yakkou Hayamihyou* 1994) Therefore, β-blockers are not always cheaper than calcium antagonists in Japan. Yamanouchi discovered and developed another calcium antagonist later. However, their third calcium antagonist project (YM430) was stopped for economic reasons. Takenaka put it thus:

> We quit [YM430] because of its cost rather than its technical concerns. That's because the prices of anti-hypertensive drugs have been severely getting lower. There are already a lot of good anti-hypertensive drugs on the

> market, and their patents have expired one after another. So, they are getting cheaper. We would have to accept a low price in this situation. Because we knew the drug would have needed massive production, we gave up from the point of view of costs. (Interview)

3.5. Discussion

3.5.1. Concepts and Compounds

Here, let us examine some of the differences and similarities between the cases of drug discovery and development in this chapter. One of the clear differences between the three cases is which came first, a theory or a substance. In the case of propranolol, the hypothesis of the beta-adrenergic receptor antagonism came before the synthesis of the compound. In the case of nicardipine, the compound came before the explanation of its action by the theory of calcium antagonism. Atenolol was searched for on the basis of Hull's hypothesis, though the hypothesis is not now thought to be correct.

However, when we look at the processes of discovery closely, each of the drugs had a prototype, namely, DCI for propranolol, practolol for atenolol and nifedipine for nicardipine. Discoveries of all these prototypes were somewhat serendipitous, that is to say, they were found to have unexpected properties: DCI had beta-adrenergic blocking activity, practolol had cardio-selectivity and nifedipine had calcium ion-channel antagonism. Moran, Black, Lands, and Fleckenstein provided the scientific explanation of the activities of these compounds, but they were not their discoverers. Therefore, it is wrong to describe discoveries in the pharmaceutical industry as always theory driven.

On the other hand, it is definitely wrong to argue that theories are of no use for discoveries in the pharmaceutical industry. On the contrary, they really help. Black's hypothesis led ICI to the discoveries of propranolol and other β-blockers. Land's theory supported the efforts to discover a better cardio-selective β-blocker after practolol. Fleckenstein's theory was nothing to do with the discovery of nicardipine, but, as we can see in the paper by the Yamanouchi's chemists and biologists

(Iwanami, et al. 1979), they obviously used many existing theories in their efforts to conduct syntheses and screening of nicardipine, and probably, so did any other researcher in the industry.

Theories and concepts are not only useful for discovering compounds but also useful for mobilising organisational resources and creating a market. Black's hypothesis made the research resources of ICI move toward the realisation of a practical β-blocker. The theory, with its evidence provided by experiments with pronethalol and propranolol, then contributed to the establishment of their clinical market. Fleckenstein's theory on calcium antagonists also greatly contributed to making the markets for nifedipine and nicardipine. The contribution of a theory to drug discovery, resource mobilization and market creation does not necessarily stem from the correctness of the theory, as was seen in the case of atenolol.

Again, it should be noted that the discovery of a compound often provides a theory with evidence and opportunity for further sophistication. This is seen in pronethalol and propranolol for the theory of two types of adrenergic receptors, in practolol and atenolol for the theory of subtypes of β-receptors, and nifedipine and nicardipine for the theory of calcium antagonists.

Thus, it is probably impossible to determine which comes first, a theory or a substance, in all the cases here. Both induction and deduction are used in order to discover a drug. However, the two cases in the UK, propranolol and atenolol, can be regarded as relatively theory driven, whereas the case in Japan, nicardipine, can be seen as relatively compound driven. Of course, because the British cases and the Japanese case are classified into different types, β-blockers and calcium antagonists, it is impossible to attribute the difference of cases simply to the difference of the place of discovery. It is interesting to note, however, that the concept of calcium antagonists, which came after the discovery of nifedipine or nicardipine, was devised in Germany, a European county. Therefore, it might not be entirely wrong to argue that this difference, between relatively theory driven and relatively substance driven, characterized the differences in pharmaceutical innovation in this area between the

UK (and probably other Western countries) and Japan. This could be attributed to the greater accumulation of (Western) scientific resources. In addition, the distance between academic research and industrial research in the medical and pharmacological area possibly had something to do with this, because basic research on the effects of calcium ions on muscle has been conducted in Japan for more than 50 years! (Ebashi 1988)

3.5.2. Paradigmatic and Normal-Scientific Discovery

Another issue is how different scientific and medical "worlds" are, before and after a discovery. If they are very different, the discovery can be called a paradigmatic discovery. If they are not so different, the discovery can be named a normal-scientific discovery. These are based on Thomas Kuhn's terminology. (Kuhn 1970) The discovery of propranolol seems close to a paradigmatic type, and the discovery of atenolol seems closer to a normal-scientific type. The consequence of paradigm-shifting discovery is destruction of an existing theory. Cannon's "sympathin E" and "sympathin I" theory was destroyed by the receptor theory and the substances, pronethalol and propranolol. Furthermore, his harmonious world of homeostasis has become dubious after learning that chemical intervention in the sympathetic nervous system might save a life. On the other hand, the discovery of atenolol did not destroy Black's theory but reinforced it, or made it more sophisticated. ICI's search was conducted with a relatively narrow target: to remove secondary properties of propranolol or practolol and to improve only the primal property, beta-blocking activity only on the heart. This property of drug is called, in technical words, specificity or selectivity. (Le Count 1982, p. 118) Specificity refers to the ability to hit only the target without any error, and selectivity refers to the ability to hit the target more than error. Thus, in the normal-scientific research, the goal is less ambitious and the area of search is narrower. Consequently, the degree of uncertainty is relatively low.

In the case of propranolol, Black's leadership was important. He linked knowledge in various disciplines, namely clinical medicine, physiology, pharmacology and

chemistry together. He realised his idea by joining a pharmaceutical company, mobilising its organisational capability and leading people towards the specific goal. His role of connecting heterogeneous actors, factors and activities can be regarded as that of heterogeneous engineer. Under the circumstance of high uncertainty, the discovery of β-blockers might not have been achieved without his leadership.

In the case of atenolol, though the scientific and technological uncertainty was probably lower than in the case of propranolol, it was not clear whether ICI's researchers could obtain the targeted β-blocker which had cardio-selectivity but not local anaesthetic activity and partial agonist activity when the research was conducted. The main task is, therefore, more specified, but it does not necessarily mean that it was easier. Because the target was better specified, it was easier for the company to pour massive effort into the search. A larger number of compounds were synthesised and examined, and one of them was chosen. Its advantages over the existing drugs were critical. Comparative studies between them had to be done to demonstrate the advantages of the new drug.

The discovery of nicardipine can be classified as normal-scientific, because its discoverers knew that nifedipine, the prototype, worked. How about the discovery of nifedipine? Its discoverers did not know why it worked when it was discovered. It was Fleckenstein who discovered the reason. Therefore, truly scientific discovery of nifedipine was completed by Fleckenstein's work. Which type is this? It can be regarded as a paradigmatic discovery. Although the previous paradigm is less obvious here than in the case of β-blocker, nifedipine provided the first example of dihydropyridine-type calcium antagonists. (Figure 3.2) Nicardipine was one of its modified compounds. The concept of calcium antagonists together with the contemporary development of other calcium antagonists such as nifedipine and diltiazem helped Yamanouchi's staff to persuade doctors.

3.5.3. Similarities between the Cases

Apart from the similarity in the interactive relationship between the theory and the

compound, there are at least two common characteristics to be noticed between the three cases. The first is uncertainty surrounding the research. All the discoveries were surrounded by a large amount of uncertainty. The application of a trial-and-error method was inevitable, because knowledge about the relationship between a chemical structure and activities in the body or the mechanism of each activity was very limited. The researchers at ICI learned the cardio-selectivity of practolol by testing. The researchers at Yamanouchi learned the anti-hypertensive activity of nicardipine by using it in clinical trials.

The second is organisational situation. According to Black and Takenaka, the atmosphere in which each of them worked was full of freedom and there was little organisational resistance to their work. It might be because their organisations were still very young. Both the ICI Pharmaceutical's laboratories at the time propranolol and atenolol were discovered, and the Yamonouchi's laboratories at the time nicardipine was discovered, were less than 12 years old. However, it might also be related simply to the times: from the early 1960s to the early 1970s. To generalize findings of this sort about pharmaceutical innovation, it is necessary to examine other cases in other settings. In the next chapter, we will discuss the cases of discoveries of anti-asthmatic drugs in Britain and in Japan.

Chapter 4: Anti-Asthmatic Drugs

4.1. Introduction

In this chapter, we examine cases of the discovery and development of several anti-asthmatic drugs. Asthma can be roughly defined as a syndrome in which there is recurrent reversible obstruction of the airways in response to stimuli which are not in themselves harmful and which do not affect non-asthmatic people. Three of the anti-asthmatic drugs examined here, salbutamol, salmeterol and procaterol, are drugs called β_2-stimulants, which stimulate beta$_2$-adrenergic receptors on the airway smooth muscle and dilate the muscle. The other two, beclomethasone dipropionate inhaler (BDP inhaler) and fluticasone propionate, are drugs called inhaled glucocorticoids (commonly called inhaled steroids), which ease the mucosal inflammation inside the airways. Salbutamol, salmeterol, BDP inhaler and fluticasone propionate were discovered by researchers at Glaxo in England, led by (Sir) David Jack and Roy Brittain. Salbutamol and salmeterol were discovered in 1966 and 1984 respectively. BDP inhaler and fluticasone propionate were originally discovered as topical glucocorticoids in 1964 and 1981. They were "re-discovered" as anti-asthma drugs in the late 1960s and in the mid 1980s. Procaterol was discovered in 1974 by a research team at Otsuka Pharmaceutical in Japan, led by Kazuyuki Nakagawa and Shiro Yoshizaki. Salbutamol (Ventolin®), salmeterol (Serevent®), BDP inhaler (Becotide®) and fluticasone propionate (Flixotide®) were first marketed in 1969, 1990, 1972 and 1993 respectively, and became the world best selling drug in each area. The worldwide sales of salbutamol and BDP inhaler in 1995 were 526 million pounds and 397 million pounds respectively. (GlaxoWellcome, *Annual Report and Accounts*, 1996) The sales of salmeterol in the world in 1997 were 406 million pounds and surpassed those of salbutamol in the same year, which were 391 million pounds. The world sales of fluticasone propionate in 1997 were 315 million pounds and close to those of BDP inhaler in the same year, which were 331 million pounds. (GlaxoWellcome, *Annual Report and Accounts*, 1998) Procaterol (Meptin®) was marketed in Japan in 1980 and became the

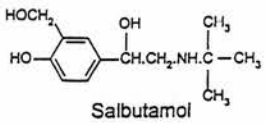
best selling bronchodilator there in 1982. Its sales in 1996 were about 15 billion yen. (*Yakuji Handobukku*, 1997)

Table 4.1: Major Events Discussed in This Chapter

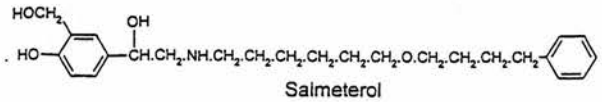
Year	Glaxo		Otsuka
	β-stimulants	Inhaled steroids	β-stimulants
1963	Research start		
1966	Salbutamol discovery	Research start	
1969	Salbutamol launch		
1972		BDP inhaler launch	Research start
1974			Procaterol discovery
1980			Procaterol launch
1981	Research restart	Research restart	
1984	Salmeterol discovery		
1992	Salmeterol launch		
1994		Fluticasone launch	

Figure 4.1: The Compounds Discussed in This Chapter

Isoprenaline



Salbutamol



Salmeterol

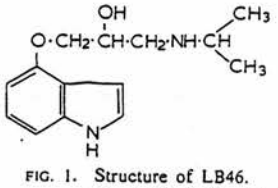
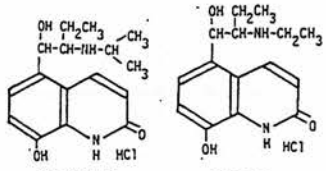
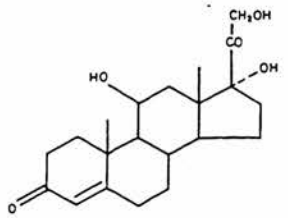


FIG. 1. Structure of LB46.

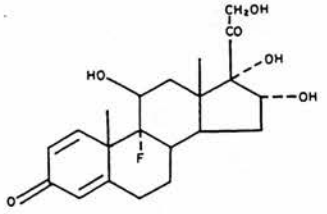
pindolol (Sandoz)



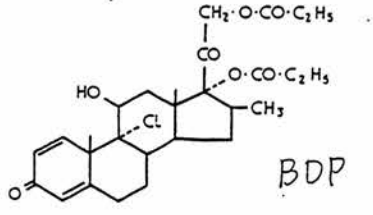
procaterol



cortisol

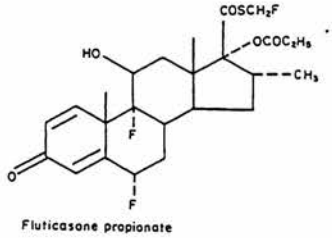


triamcinolone



BDP

9-α-chloro-11β,17α,21-trihydroxy-16-β-methylpregna-1,4-diene-3,20-dione, 17,21-dipropionate



Fluticasone propionate

4.2. Salbutamol

During World War II, H. Konzett at C. H. Boehringer in Ingelheim, Germany, found that a new analogue of adrenaline had a strong bronchodilating action with fewer side effects than adrenaline itself. (Konzett 1940a, b) Knowledge of this discovery became generally available after the war when the US State Department was investigating the wartime work carried out by German chemical manufacturers. The compound, isoprenaline (isoproterenol in the US), was introduced clinically in 1951. It was considered as the drug of choice for the relief of acute asthmatic attacks for the next twenty years. (Sneader 1985, pp.102-103) However, the introduction of its aerosol form during the sixties led to a large number of deaths because of the effects of overdose on the heart due to the lack of selectivity of isoprenaline. (Greenberg and Pines 1967; Inman and Adelstein 1969) Another disadvantage of isoprenaline was that it was too short acting. (Sneader 1985, p.103; Brittain, Jack and Ritchie 1970, p.200) Several pharmaceutical companies tried to overcome these disadvantages of isoprenaline. In 1961, C. H. Boehringer developed a new drug called orciprenaline, which was different from isoprenaline only in the position of a hydroxyl group in the molecule. Like isoprenaline it was active about equally on bronchial muscle and the heart but it was more stable in the body. Therefore it was longer acting than isoprenaline, though it was less potent. In 1964, Mead Johnson Company in the US discovered another adrenaline analogue, soterenol. Although soterenol was an effective and long-acting bronchodilator, it was found to be toxic in animals and was not marketed. (Sneader 1985, pp.103-104; Brittain, Jack and Ritchie 1970, pp.206-213; Jack personal communication, July 2000)

It was Glaxo that had the greatest success in solving the problem. David Jack and his fellow researchers at Allen & Hanburys in England, which had been a subsidiary of Glaxo since 1958 (Davenport-Hines and Slinn 1992, pp.170-172, p.198), started their research on β-stimulants in 1963. Their early objective was a long-acting β-stimulant to replace isoprenaline. Jack, who joined the company as the research director in 1961, explained his situation at that time:

> I started with 122 R&D staff after being assured by the managing director of Allen & Hanburys and the chairman of Glaxo that the staff would be increased to 200 because this was the minimum needed to find and develop a significant new medicine. A second assurance was that we in Allen & Hanburys would be given at least 5 years to show if we would do something useful. (Interview with Sir David Jack)[1]

Jack chose the area of anti-asthmatic drugs as one of the targets at his laboratories because asthma was a very common illness but its treatment was underdeveloped at the time. Jack put it:

> [T]he secret of success in the pharmaceutical business is to find better medicines for common illnesses. ... It's so obvious, but people forget it. I considered asthma in 1963 because it was a badly treated common serious illness. Isoprenaline, the most effective bronchodilator was too short-acting and was a powerful cardiac stimulant. Theophyline, the best available orally active bronchodilator also had use-limiting side effects. There was clearly need for a better bronchodilator.
> The other drugs which were available by 1962 were anti-inflammatory steroids, analogues of cortisol. And by then, prednisone, prednisolone were available and so too, I think, would be dexamethasone and betamethasone. These drugs were of great value in asthma because they control the inflammation within the lungs. Unfortunately, although they were effective, they had major systemic side effects. (Interview)

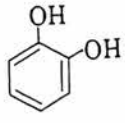
The search for a better β-stimulant was, thus, the first work the Allen & Hanburys researchers did in the anti-asthmatic area. At an early stage in the research, Larry Lunts, a chemist in the research team, reached the idea that inhaled isoprenaline was short acting because it was rapidly metabolised by catechol specific mechanisms. Catechol is a chemical group (Figure 4.2) included in isoprenaline molecules. Therefore, he considered that non-catechol analogues of isoprenaline would be expected to be longer acting. He replaced one of the two hydroxyl groups of the ring by a CH_2OH group. The resulting compounds are called saligenin analogues of isoprenaline. Lunts made several saligenin analogues, side chains of which were different from each other in structure. (Lunts 1985; Jack 1996, 6) In 1966, five years after Jack's agreement with his boss, the research team found that one of the analogues had not only the expected longer duration of action (3 – 4 hours against 1

[1] This interview with Sir David Jack was conducted on 26 April 1999.

– 1.5 hour in isoprenaline), but also unexpected high selectivity for the bronchi: the latter property meant that the compound had much less side effect on the heart, which constituted the other major disadvantage of isoprenaline. The compound was named salbutamol. (Hartley, et al. 1968; Brittain et al. 1968; Cullum et al. 1969; Jack 1998, p.141) A number of clinical studies in humans confirmed the longer duration of action and the selectivity of salbutamol in comparison with isoprenaline. (E.g. Choo-Kang, Simpson and Grant 1969; Chatterjee and Perry 1971; Tara, Kellomaeki and Pylaes 1971; Conolly et al. 1971; Schmann and Herxheimer 1971) Although salbutamol was effective by mouth, the duration of action was found to be less than when it was given by inhalation. (Simpson 1971; Minetti 1971)

The selectivity of salbutamol was strong evidence for the theory formulated by Lands and his colleagues at Sterling Winthrop in the US that beta-adrenergic receptors could be subdivided into $beta_1$ and $beta_2$ subtypes. There are much more $beta_1$ subtypes than $beta_2$ in the heart, whereas there are much more $beta_2$ subtypes than $beta_1$ in the airway. (Lands et al. 1967; Cullum et al. 1969, 150) Salbutamol was found to be a $beta_2$-selective stimulant. Jack wrote later: "We were naturally disappointed that our discovery of selectivity within β-adrenergic effects had been anticipated but were comforted by the fact that salbutamol was clearly a better drug than any of the catecholamines." (Jack 1989, 173) Because salbutamol was $beta_2$ selective, its short-term adverse effects were little. (Chatterjee and Perry 1971; Minette 1971; Conolly et al. 1971) Salbutamol was marketed in 1969 and became the most commonly used bronchodilator in the world (Sneader 1985, p.104; Jack 1998, p.143; Website of GlaxoWellcome), though controversy over the safety of the long-term, regular use of salbutamol and other $beta_2$-selective bronchodilators arose later. This is discussed in Section 4.4.2 in this chapter.

Figure 4.2: Structure of Catechol



4.3. Beclomethasone Dipropionate Inhaler (BDP Inhaler)

The next project for the Allen & Hanburys' researchers after the discovery of salbutamol was the search for an anti-inflammatory agent to ease the inflammation inside the airways of asthma patients, which is another main cause of asthma. They focused on glucocorticoids, a group of anti-inflammatory steroid hormones, which are often called just "steroids." (Jack 1996, 7)

The clinical value of glucocorticoids as anti-inflammatory agents was generally known after a report that Philip Hench at the Mayo Clinic in the US had successfully used cortisone, one of glucocorticoids, for the treatment of rheumatoid arthritis in 1948 to 1949. (Hench et al. 1949; Sneader 1985, p. 222) Cortisone was at first presented as a "miracle cure" because of its drastic anti-inflammatory action. As a consequence, Hench and his colleague, Edward Kendall won the Nobel Prize in 1950. Shortly after this, however, the reputation of cortisone began to decline partly because it was found that cortisone also causes serious side effects due to its multiple activities at the various parts of the body, and partly because its supply was limited and its price was too expensive. (Le Fanu 1999, pp. 22-23) Much politics ensued involving in rheumatologists, governments, funding organizations, pharmaceutical companies and patients before cortisone was established as a drug. (Marks 1992; Cantor 1992) Development of other applications, especially dermatological, ophthalmologic and anti-asthmatic uses restored and even enhanced the usefulness of cortisone. Many of these applications were topical uses, in which side effects were less significant. (Le Fanu 1999, pp. 23-26) In the 1950s, several analogues of cortisone were synthesized, aiming at enhancing potency and selectivity on glucocorticoid receptors rather than mineralocorticoid receptors: fludrocortisone by Squibb, prednisone and prednisolone by Schering (US), methylprednisolone by Upjohn, triamcinolone by Lederle, dexamethasone by Merck and betamethasone by Schering (US). The selectivity of glucocorticoids was important because their binding with mineralocorticoid receptors causes unwanted side effects. Thus, Dexamethasone and betamethasone, both of which were marketed in the late 1950s, were more potent and more selective than their predecessors, for example,

prednisolone, which had been introduced in the mid-1950s. (Sneader 1985, pp.223-226)

The application of cortisone for the treatment of asthma was reported as early as 1950. (Carey et al, 1950) However, the problem of how to reduce systemic side effects prevented the application of cortisone and its analogues for the long-term treatment of asthma except in severe cases. (Wilcox and Avery 1973, 85, 88) Inhalation of corticoids had been tried since 1951 but these trials did not bring good results even when dexamethasone, a strong glucocorticoid, was used. Systemic side effects were observed at effective dosage levels of the drug. (Morrow Brown, Story and George 1972, 585; Lal et al. 1972, 315; Editorial, *The Lancet* 1977, 2, 695) In the 1960s, the topical application of corticoid derivatives, such as triamcinolone acetonide (Sneddon 1976, 193) and betamethasone valerate (Williams, et al. 1964), to skin diseases was successfully introduced. Based on these successes, around 1966, the application of such topical anti-inflammatory steroids inside the airways by inhalation was proposed within the Glaxo group by Wilfred Simpson at Allen & Hanburys and by Gordon Philips and Eric Snell in Glaxo Laboratories, independently. (Jack 1996, 7)

Glaxo had many years experience in manufacturing cortisone and its analogues. (Davenport-Hines and Slinn 1992, pp.186-190, p.196; Elks and Phillipps 1985, pp. 176-179; Sneader 1985, p.223) Research on glucocorticoid had also been conducted in the Glaxo group. Betamethasone valerate, one of the successful topical glucocorticoids, was synthesized there. Following this, Glaxo researchers synthesized a new glucocorticoid called beclomethasone dipropionate in 1964. (Caldwell et al. 1968; Fukai 1988, pp.549-550) These experiences and the consequent knowledge, skills, facilities and other material resources possessed, individually and collectively, by the organization, probably played a significant role in connecting the needs of anti-inflammatory agents in asthma treatment with the idea of using topical glucocorticoids by inhalation.

The proposal to use topical glucocorticoids by inhalation, however, posed several questions: Would the bronchial mucosa resemble the skin in being sensitive to their anti-inflammatory action? Would the treatment favour the spread of infection in the lung? Would it cause all the kinds of side effects associated with glucocorticoids? (Jack 1990, 9; Jack, interview) Anti-inflammatory activity of glucocorticoids was (and is still) not fully understood. (Jack 1998, p.159; Le Fanu 1999, p.28) Tests in animals and in humans played a key role in the selection of glucocorticoids for use in asthma. In the case of the use of glucocorticoids on the skin, there was an established test called the McKenzie skin-blanching test (McKenzie and Stoughton 1962), which was found to give sufficiently accurate forecasts of clinical potency because it used humans themselves without hurting them. (Elks and Phillipps 1985, p. 176; Jack 1998, p.159) However, it was questionable whether this was relevant to their use inside the airways by inhalation. Despite these uncertainties, Jack and his colleagues went ahead. They chose beclomethasone dipropionate (BDP) as an inhaled steroid, because it was more potent than betamethasone valerate and relatively limited in systemic activities. The topical anti-inflammatory activities were measured with the McKenzie and Stoughton skin-blanching test, and the researchers believed that the test also represented the activity inside the airways. The systemic activities were measured through suppression of early-morning plasma cortisol levels in volunteers. The weakness of systemic activities of BDP was later explained by its inactivation due to oxidation in the liver during first pass metabolism. (Caldwell et al. 1968, 111-112; Jack 1998, pp.159-161) Then, they tested the drug in dogs. Six months of administration of BDP by mouth and by inhalation made the dogs develop a condition similar to Cushing disease, in which there is too much secretion of hydrocortisone. However, at the end of the experiment, the lungs of the dogs were found to be normal, and infection had not been a problem. They were encouraged by the results to proceed to human trials. (Jack 1990, 9) Clinical trials in humans produced favourable results. (Morrow Brown, Storey and George 1972; Clark 1972; Lal et al. 1972) Beclomethasone dipropionate inhaler was marketed in 1972 and became one of the major treatments of chronic asthma during the 1980s and 1990s. (Jack 1990, 9; Jack 1998, pp.159-160)

4.4. Salmeterol

4.4.1. Discovery and Development of Salmeterol

With the launch of salbutamol in 1969 and of BDP inhaler in 1972, Glaxo obtained a combination of drugs against the two major causes of asthma: constriction of the airways and mucosal inflammation inside them. However, once the two drugs solved the initial problems – the treatment for the two causes on a basic level – a new set of problems on a higher level appeared.

Salbutamol had several problems. First, its duration of action, 3-4 hours is too short to prevent worsening of asthma during the night. The level of adrenaline in the blood drops during the night, and asthma patients often suffer severe attacks when this happens. (Jack 1998, p.144; Jack interview) Second, a number of β-stimulants such as terbutaline, fenoterol and pirbuterol were marketed after salbutamol and competition in the area became severer. Terbutaline, discovered and developed by Astra in Sweden, was the most powerful rival. (Sneader 1985, pp.104-105; Jack interview) Third, a 12-year delay in its launch in the US lessened salbutamol's competitive advantage in the new important market. (Jack 1991, 504) In addition, the patents of salbutamol were getting close to their expiration. (Jack interview)

Jack and his colleagues tried to discover a better orally active β-stimulant during the 1970s. They also tried to find a better bronchodilator based on other physiological mechanisms. However, they failed in both. (Jack 1998, p.144; Jack 1991, 504; Jack interview) Furthermore, Jack and some of his colleagues were at the time involved in two other big projects: H2 antagonists and 5-hydroxy-tryptamine (5HT, serotonin) related agents. (See Section 5.3. Ranitidine; Jack 1989, 182; Jack interview) Therefore, it was in 1981, the year when a conference was held in Boston to promote salbutamol in the US, when Jack had to think about the future of brochodilators, and he "concluded that the desired drug would have to be given by inhalation if side effects were to be avoided and would have to be much longer acting than salbutamol

and similar β_2-agonists to prevent nocturnal attacks of asthma." (Jack 1998, p.144; Jack 1991, 504-505)

Jack then considered how the prolongation of action might be achieved with an inhaled β-stimulant. The target duration of action was at least 8 hours to prevent nocturnal asthma worsening. (Jack 1998, p.145) He considered two ways of prolonging duration. One was to make a drug which would be more slowly absorbed from the bronchi. The other was to make a drug which sticks firmly at its site of action in the receptor protein and remains efficacious for a long time. He chose the latter approach because it "was simpler and seemed more likely to work." (Jack 1991, 505) The hypothesis for achieving this was to keep the ring structure of a β-stimulant molecule with high affinity for the adrenaline binding site in the receptor protein, and to make a large flexible non-polar side chain to ensure selectivity of action and to anchor the drug with the receptor protein. (Jack 1996, 10; Jack 1998, p.145)

Jack believed that there were two types of agonism: in type 1 agonism the affected cells were capable of responding continuously to continuing stimulation, whereas in type 2 agonism the cells, having responded to an effective stimulus, must recover before it can respond to another. (Jack 1977; Jack 1991, 504) He also believed that adrenergic agonism must belong to type 1 agonism because adrenaline remains efficacious despite being continuously present in the extra-cellular fluid. (Jack 1998, p.145) Although his classification of agonism seems not to have been generally used in academic literature, it did lead him to the search for a better β-stimulant. (Jack 1991, 504)

Based on this thinking, Jack commenced the research project in 1981. However, some of his colleagues were doubtful about the approach, because there was a large amount of literature (E.g. Conolly et al. 1971; Jenne 1977; Greenacre, Schofield and Conolly 1978; Plummer 1978; Harden 1983, 25) on desensitisation of β-receptors exposed to β-stimulants for a long time and reports of tolerance to β-stimulants in patients. (Jack 1991, 505; Jack 1998, p.145) On the other hand, there were some studies (Larsson, Svedmyr and Thiringer 1977; Peel and Gibson 1980; Shepherd,

Henzel and Clark 1981) that did not find the tolerance to β-stimulants by regular use of them. Persuading the doubtful researchers was not practical because scientific controversy over the issue obviously existed: "The only way to settle the matter was to find and test the desired drug." (Jack 1991, 505) Jack, as the research director, showed his leadership by insisting that they test his hypothesis. He put it:

> [Some colleagues] said, "You're wasting your time, David." ... How did I persuade them? I told them to do it. (laugh) But then when they found that what I was saying was not mad, it then became theirs. But at the beginning I had to tell them to do it. (Interview)

Larry Lunts, who was the originator of salbutamol and responsible for chemistry in the new project, decided to seek the required drug in analogues of salbutamol with increasingly large non-polar side chain, based on Jack's hypothesis. The rates of onset and offset of action of these analogues were measured using guinea pig tracheal muscle. Interest in the team rose sharply when it was found that this preparation was not easily desensitised by continuous superfusion with isoprenaline or other β-stimulants, and that the rates of onset and offset of action of the analogues varied considerably. These findings supported Jack's hypothesis. The researchers who had at first doubted the idea became convinced that it would work. By painstaking optimisation, they succeeded in finding salmeterol, a selective, very long acting (more than 12 hours) β-stimulant with a long non-polar side chain, in 1984. (Jack 1998, p.146; Jack interview; Bradshaw et al. 1987; Ball et al. 1987; Brittain, Jack and Sumner 1988; Ball et al. 1991) The potency, the duration of action and the safety of salmeterol were confirmed in clinical trials. (Britton et al. 1992; Brogden and Faulds 1991; Jack 1998, pp.163-166) It was also suggested that the unusual effectiveness of salmeterol might be due in part to its anti-inflammatory activity in the airways. (Twentyman et al. 1990; Butchers, Vardey and Johnson 1991; Whelan and Johnson 1992) Salmeterol was marketed in 1992. (Jack 1996, 12)

4.4.2. Salmeterol and the β Stimulant Controversy

When salmeterol was marketed, there was a hostile atmosphere to regular use of β-stimulants. (Jack 1996, 12; Jack 1998, pp.162-163) There had been a long lasting controversy over regular, long-term use of β-stimulants. (*Lancet* editorial 1990; Löfdahl and Svedmyr 1991; Chung 1993; Sears and Taylor 1994; Boulet 1994; Crane et al. 1995; Ernst 1998) After the high incidence of death during the use of isoprenaline aerosol, doubt arose over tolerance to β-stimulants during the long-term, regular use of β-stimulants. Some researchers concluded that the mortality was due to the side effects on the heart by overdose of isoprenaline, a nonselective β-stimulant. (Greenberg 1967) However, other researchers thought that it might be due to the resistance to β-stimulants which was built by their regular use. (Conolly et al. 1971; Jenne 1977; Greenacre, Schofield and Conolly 1978; Plummer 1978; Harden 1983, 25) There were also studies which supported regular use of β-stimulants. (Larsson, Svedmyr and Thiringer 1977; Peel and Gibson 1980; Shepherd, Henzel and Clark 1981; Harvey and Tatterfield 1982) They could not reach a consensus because differences in test situations such as *in vivo* versus *in vitro* (Shapherd Henzel and Clark 1981 vs. Greenacre, Schofield and Conolly 1978) and normal subjects versus asthma patients (Holgate, Boldwin and Tatterfield 1977 vs. Harvey and Tatterfield 1982) made the controversy more complicated. However, this controversy might have faded out had it not been for the incidence of a sharp increase of asthma mortality in New Zealand from the mid 1970s. (Taylor and Sears 1994, 261-262)

The "epidemic" of asthma mortality since 1977 was internationally reported in the early 1980s. (Jackson et al. 1982; Grant 1983) The medication was suspected as its cause early on: at first, combined treatment with oral theophylline and β-stimulants, and then β-stimulants themselves. (Grant 1983) In 1989, the first case-control study on the relationship between the regular use of β-stimulants and asthma mortality by researchers at Wellington School of Medicine (New Zealand) was published. (Crane et al. 1989) The authors claimed that use of fenoterol, a powerful β-stimulant developed by Böhringer Ingelheim, by inhaler increased the risk of death in asthma. This study was criticised by several groups in terms of both methodology and

interpretation. (O'Donnell et al. 1989; Buist et al. 1989; Sacket, Shannon and Brownman 1989; Poole, Lanes and Walker 1990) The two important points of criticism were whether the regular use of fenoterol was the main cause of asthma mortality or just the marker of fatal asthma, and whether the relationship with asthma mortality was limited to fenoterol or a general problem for β-stimulants as a class. The Wellington group conducted further case-control studies because of this criticism, but the results supported their original arguments: it was regular use of fenoterol that caused the epidemic in New Zealand. (Pearce et al. 1990; Grainger et al. 1991) Other researchers also supported this and suggested that it might be due to the very large dose and the lesser $beta_2$ selectivity of fenoterol. (Wong et al. 1990; *Lancet* editorial 1990; Löfdahl and Svedmyr 1991)

One major opposing group of the Wellington study was researchers at Böhringer Ingelheim, the manufacturer of fenoterol, (Staudinger and Haas 1992a; Staudinger and Haas 1992b; Schuijt and Staundinger 1995) and advisory researchers of the company. (Buist et al. 1989; Spitzer and Buist 1990; Spitzer et al. 1992; Suissa et al. 1994) The advisory researchers conducted their own large-scale case-control studies in Canada. (Spitzer et al. 1992; Suissa et al. 1994) Although they admitted that there was strong correlation between the regular use of fenoterol and asthma mortality, they claimed that fenoterol might be a marker of severe asthma because it tended to be prescribed for that due to its high potency, and that there were no significant differences in selectivity between fenoterol and other β-stimulants, particularly salbutamol, but overdose of β-stimulants might cause the serious side effects. According to them, fenoterol was prone to be overdosed because its originally recommended dose was larger than that of salbutamol despite its relative potency in beta stimulation. They insisted that β-stimulants were safe when they were used properly, and that β-stimulants should be used with glucocorticoids to control inflammation inside the airways because this could not be done by β-stimulants. Some other researchers shared their view. (Blauw and Westendrop 1995; Wanner 1995)

Another major opposing group of the Wellington study was Malcolm Sears and his colleagues at University of Otago Medical School, who claimed that although the relationship between regular use of β-stimulants and asthma mortality was causal, this was not limited to fenoterol alone but was potentially applicable to any other β-stimulant, including salbutamol and salmeterol. They insisted that asthma mortality was not due to cardiac side effects of less selective β-stimulants but due to worsening asthma caused by regular use of β-stimulants. (Sears et al. 1990; Sears and Taylor 1992; Sears et al. 1992; Taylor et al. 1993; Taylor and Sears 1994; Sears and Taylor 1994; Sears 1995)

The argument by Sears and his colleagues caused further debate because it claimed that all β-stimulants should not be used regularly and that emerging longer acting β-stimulants such as salmeterol might have the same risk as regular use of short acting β-stimulants. Several researchers supported their view. (Crompton 1991; van Schayck et al. 1991) On the other hand, there were also several critics, including the Wellington group and researchers at Glaxo, of the generalisation of the results from fenoterol to β-stimulants as a class. (Palmer and Jenkins 1991; Dahl 1991; Crane et al. 1991; Clark 1991; Chapman Kesten and Szalai) In particular, researchers at Glaxo, based on their post-marketing clinical studies of salmeterol, strongly opposed the claim of the Otago group that salmeterol might exacerbate asthma. (Jenkins et al 1991; Shepherd, Jenkins and Alexander 1991; Castle et al. 1993) Sears' group, William Inman at the Drug Safety Research Unit, which was conducting a post-marketing surveillance study of salmeterol, and two other groups argued that Glaxo's study underestimated mortality of asthma related to salmeterol. (Inman 1993; Bunney 1993; Crompton 1993; Sears and Taylor 1993) The Glaxo researchers defended themselves. (Fuller et al. 1993) However, the guidelines on the management of asthma issued by the British Thoracic Society in 1993 showed a cautious attitude about regular use of bronchodilators, especially, salmeterol. It advised that regular use of bronchodilators should come after high dose inhaled steroids and that long-acting bronchodilators like salmeterol should be used for more serious cases only, because of the uncertainty about regular use of bronchodilators. (The British Thoracic Society 1993, pp. S4-S5, pp. S10-S11, p. S18)

There was another strand of the β-stimulant controversy. Jeff Garnett and his colleagues at Green Lane Hospital in Auckland, New Zealand, insisted that increasing financial barriers to primary health care against a background of social and economic decline were likely to have contributed to asthma morbidity and mortality in New Zealand. They also argued that the reduction in asthma mortality in the 1980s was mainly due to an improvement in utilisation of hospital services, and that the further reduction in asthma mortality since 1989 would be best explained by increase in use of inhaled steroids and by improvement in management of asthma, that is, more careful treatment for asthma. (Garnett et al. 1995) Both the Wellington group and the Otago group opposed this view and argued that the socio-economic factor was not the main cause but regular use of fenoterol (or β-stimulants) was. (Crane et al. 1995; Taylor and Wong 1995) On the contrary, there were also studies which strongly doubted the relationship between use of β-stimulants and death from asthma. (Mullen, Mullen and Carey 1993)

The β-stimulant controversy seemed to be fading in the late 1990s. This decline may be partly because the "epidemic" in New Zealand ended, partly because simultaneous use of β-stimulants and inhaled steroids provided every party involved in the debate with a satisfying answer in practice, and partly because long-term clinical trials of long acting β-stimulants, especially salmeterol and formoterol, did not find exacerbation of asthma when they were used with inhaled steroids. The end of the New Zealand "epidemic" of asthma death, in fact, led to another debate. The Wellington group sought the cause of reduction of mortality from the withdrawal of fenoterol. (Pearce et al. 1995) Researchers at Böhringer Ingelheim and the advisory researchers of the company argued that the cause was due to advances in patient education and adequate anti-inflammatory treatment. (Schuijt and Staudinger 1995; Ernst and Suissa 1995) As mentioned above, Garnett and his colleagues emphasized the socio-economic factor as one of the major cause of the reduction. (Garnett et al. 1995) However, this debate was less heated. It is probable that the end of the epidemic was less interesting for researchers than its outbreak.

The second factor which probably contributed to the quasi-closure of the debate was that there was a consensus over the practical problem of how to manage asthma: simultaneous use of β-stimulants and inhaled steroids. Almost all researchers recognised and often argued that inhaled steroid should be used to treat airway inflammation, which causes asthma symptoms. Therefore, they would not oppose concurrent use of β-stimulants and inhaled steroid. In fact, most of them did promote the treatment. (Crane et al. 1995; *Lancet* Editorial 1990; Staudinger and Haas 1992a; Ernst and Suissa 1995; Sears et al. 1992; van Schayck and van Herwaarden 1993; Rees 1991; Chung 1993; Heino 1994; Boulet 1994; Greening et al. 1994; Woolcock et al. 1996; van der Molen 1996; Wilding et al. 1998; Jack 1998) The British Guidelines on Asthma Management and its Japanese counterpart also adopt this treatment. (The British Thoracic Society et al. 1997; Makino, Koshou and Miyamoto eds. 1998, p. 69)

The third plausible factor in the decline of the controversy was the accumulated results of the use of long acting β-stimulants. In 1994, another long-term study of salmeterol, supported by Glaxo, showed that there was no evidence that regular use of salmeterol contributed to asthma exacerbation, when using it with BDP. (Greening et al. 1994) The Drug Safety Research Unit, which had initially opposed Glaxo's results, also stated that there was no evidence that salmeterol contributed to the deaths from asthma, after completing the study. It explained that its early overestimation of asthma mortality in patients using salmeterol was due to the assumption that deaths would be evenly distributed throughout the study, which was not the case because 39 of the 73 deaths occurred in the first seven months of 25 month long study. (Mann 1994) Based on these studies, the British guidelines on asthma management revised in 1995 and issued in 1997 showed a somewhat more favourable attitude to salmeterol. It was recommended that low dose inhaled steroids plus salmeterol be regarded as an alternative in step 3 treatments, while the former guidelines placed the drug after step 4 treatments, which is for more severe asthma. (The British Thoracic Society et al. 1997, p. S2, p. S11) Several studies supported the safety of salmeterol. (Woolcock et al 1996; Wilding et al. 1997) A study on formoterol, another long acting β-stimulant developed by Ciba-Geigy, also claimed

that its use with inhaled steroids improved patients' condition. (van der Molen et al. 1996) There were also studies warning that use of salmeterol might cause subsensibility to salbutamol (Grove and Lipworth 1995), and that use of salmeterol could delay recognition of increasing airway inflammation. (McIvor et al. 1998) However, the attitude to salmeterol seems to have become less hostile recently. In 1997, sales of salmeterol for the first time became more than those of salbutamol. Despite this, it is important here to notice that the β-stimulant controversy obviously limited the sales of salmeterol. (Ernst 1998)

4.5. Fluticasone Propionate

Although inhaled BDP was found to be an effective and generally safe treatment for asthma, it had significant systemic side effects when used in high dosage. Because of this and because the patents for inhaled BDP, like those of salbutamol, would expire in less than 10 years, Jack was forced in the early 1980s to consider how it might be replaced by a superior drug. What was required was an inhaled glucocorticoid with more intense anti-inflammatory activity than inhaled BDP in the airways but devoid of systemic side effects at therapeutic dosage. He consulted the Glaxo list of potential topical glucocorticoids and chose fluticasone propionate as a candidate. (Jack interview and personal communication) In the early 1980s, G. H. Phillipps at the company discovered this during an unsuccessful search for a topical steroid which did not cause skin thinning. (Dutch patent application 81 00707, 1981; US patent 4335121, 1982; Jack personal communication) Fluticasone propionate had been shown to be about twice as active as BDP in the McKenzie and Stoughton skin-blanching test in humans but almost inactive after oral administration in rats and mice. (Phillipps 1990; Jack 1998, 160; Jack personal communication)[2] The compound was later found to be similarly inactive orally in humans and the reasons for this was attributed to the first pass hydrolysis in the liver into two inactive fragments. This lack of oral activity was favourable for the treatment of asthma,

[2] The intense skin-blanching activity was significant because it indicates tight binding of the steroid to its receptor protein and, therefore, high topical anti-inflammatory activity. Oral inactivity in mice was unusual because that species is extremely sensitive to glucocorticoid steroids. (Jack personal communication)

because part of the inhaled drug absorbed from the gut would not cause unwanted systemic side effects. (Jack 1998, pp.160-162; Jack personal communication)

Fluticasone propionate was thus chosen for clinical trials and shown to be twice as active, on a weight basis, as BDP and at least as safe as BDP in asthmatic patients. (Lundback et al. 1993; Barns et al. 1993; Holliday, Faulds and Sorkin 1994) It was also reported that treatment with fluticasone propionate was less associated with reduction in leg growth velocity in children than that with BDP, which implied less systemic effects of fluticasone propionate. (Wolthers and Pederson 1993) The high potency of fluticasone propionate was explained by its persistent binding to the glucocorticoid receptor protein. (Högger and Rohdewald 1994) Fluticasone propionate was marketed in 1994 and became a very successful inhaled steroid. (Jack 1998, p.162)

Thus, the combination of salmeterol and fluticasone propionate became a successor to that of salbutamol and BDP. By analogy with the game of poker, Jack compared each combination to a "full house" consisting of a selective beta$_2$ stimulant (equivalent to two of a kind) and a topical glucocorticoid steroid (equivalent to three of a kind). Both are a "full house" but the former is a better one. However, this idea was not intended from the beginning but emerged and evolved in the research and development process. Jack put it:

> **Jack**: And don't forget that a full house is a good hand, but is not the best hand in poker. Similarly these combinations are unlikely to be the best hand for asthma. Better treatments are likely to be discovered.
> **Hara**: Did you aim at a full house?
> **Jack**: Not at the beginning. All of this happened with increasing understanding of the problem. One profound thing that not everybody knows is that we think with what we know. As years go by and one "lives" with asthma, knowledge and, with it, understanding becomes more and more, increases and increases, and the way you think is correspondingly changed. OK? (Interview)

4.6. Procaterol: A Beta-Stimulant Made in Japan

Otsuka Pharmaceutical in Japan began its research on adrenergic drugs in 1971. Until then, the company had mainly been a manufacturer of nutritional preparations for clinical uses and over-the-counter (OTC) products. (Otsuka 1999, p.32) A little time before the establishment of its own laboratories, the company planned to manufacture an existing β-blocker, which was at that time a new type of drug. However, the supply of a key material was stopped by the parent company of the supplier and the plan failed. When Otsuka decided to start their own research, therefore, they chose a β-blocker as their first target. (Miwa, interview[3])

A research team at Otsuka Tokushima Laboratories led by Kazuyuki Nakagawa started research on β-blockers in January 1972 and, one month later, succeeded in the discovery of a β-blocker, cartelol. (Nakagawa et al. 1974; Nakagawa interview) This was the first product of their research and was marketed in 1980. In the synthesis, they chose pindolol, which was synthesized by a Swiss company, Sandoz, in 1964 (Saameri 1967; Hill and Turner 1969; Fukai 1988, p.232), as the lead compound. This was because there had already been a lot of analogues of propranolol whereas pindolol analogues seemed less exploited. (Nakagawa, interview) They tried to replace an indole group of pindolol structure and chose a dihydrocarbostyril group, partly because it has a proton which an indole group also has, and partly because it has a shape as if the side chain of acetaminophen were cycled, which seemed to be as active as acetaminophen but less toxic than it. This approach was found to be successful, and Nakagawa and his colleagues were able to find compounds which blocked β-receptors. (Nakagawa, interview) At least 45 derivatives were synthesized and cartelol was chosen as a drug. (Nakagawa et al. 1974)

Beta-blockers, which attach to beta-adrenergic receptors but do nothing to them, and β-stimulants, which also attach to the receptors and stimulate them as if they were adrenaline, are clinically opposites but chemically very similar. This means that if

[3] This interview with Dr Kazuyuki Nakagawa, the former head of chemical research, Mr. Hideyuki Miwa, the director of research and development, and Mr Shinya Tashiro, the respiratory group leader in the development department was conducted on 9 November 1999.

cartelol is effective as a β-blocker, there may be an effective β-stimulant among its analogues. Additionally, cartelol was found to be well distributed to the trachea. This property was advantageous as a bronchodilator. Based on these ideas, they started the research on β-stimulants in April 1973. Although the research was temporally suspended because the researchers had to support the development of cartelol, it did not take a long time for them to find a β-stimulant. The search for a β-stimulant was relatively easy, according to Nakagawa. This was because they already had the basic structure, a dihydrocarbostyril group, the same as cartelol, and it was the side chain that had to be devised. (Nakagawa, interview) There were several effective β-stimulants at that time. Shiro Yoshizaki, the project leader, and his colleagues at Otsuka examined these existing β-stimulants, for example isoprenaline, salbutamol, terbutaline and isoetharine, and synthesized a series of compounds with carbostyril and dihydrocarbostyril groups. (Yoshizaki et al. 1976; Nakagawa, interview) Despite the interruption, they found a highly potent compound as early as February 1974. This was the ninth compound in the research. This compound, with a carbostyril group and an isoetharine-type side chain, was at first named OPC-2009. After the synthesis of OPC-2009, the researchers continued to make various derivatives partly because there might be a better one, and partly because it was needed to ensure sufficient patent coverage so that rival companies could not make similar compounds to compete against Otsuka's one. By April 1974, they had synthesized about 50 compounds. About 30 of them had strong β-receptor stimulating activity, and two of them were considered as the final candidates for development: OPC-2009 and OPC-2030. (Nakagawa, interview; Takayanagi et al. 1977)

OPC-2009 was more active than OPC-2030, but its activity on the heart was also stronger than that of OPC-2030. As a result of discussion among researchers and staff in charge of development, OPC-2009 was eventually chosen. It was said that the opinion of Akihiko Otsuka, the then Tokushima Plant Manager who also led the laboratories, had a strong influence on the decision. Otsuka was a member of the owner family of the company and later became its president. The reason for the choice was that it was probably better that the efficacy was outstanding for clinical trials and for marketing. However, this was a subtle problem. Nakagawa put it:

> It was very hard question. If we had chosen OPC-2030 and had failed, nobody would have known how different the results would have been if we had chosen OPC-2009. This is because there was just one chance. ... Japanese people then had, perhaps still have, a tendency to prefer mild drugs with fewer side effects to very potent drugs with some side effects. Therefore, OPC-2030 might have been successful. (Nakagawa, interview)

According to Nakagawa, there were few organizational obstacles in the development of OPC-2009, now renamed procaterol, because there was only one other project. The main obstacles were more technological ones. These occurred in the development of the tablets and the inhaler of the drug. Procaterol was easily soluble in water and this property was convenient to make a variety of preparations. However, because the drug was so active, it was necessary to ensure that each tablet or puff of inhaler equally contained a specific, very small amount of drug. There were two major technological problems there. One was to achieve this equality, and the other was to measure the equality. They made a considerable effort to solve these problems and were able to cope with them. In particular, the establishment of liquid chromatography in the 1970s helped the solution of the latter problem. Another problem was the interaction between the drug, and a very small amount of water or impurities contained by diluents, packaging materials and components of inhalers. Collaboration with suppliers of various materials was important. (Nakagawa, interview)

The next problem in the development of procaterol was how to proceed to clinical trials because the company had little experience in clinical trials for a new drug. They asked Yuichi Yamamura, a professor at Osaka University and an authority on the immunology and allergology in Japan, to be the chairman of the clinical trial committee of procaterol. Yamamura accepted it and organized the committee. (Miwa, interview) Otsuka's staff described this process:

> **Miwa**: It was very important to ask Professor Yamamura to organize the clinical trials.
> **Tashiro**: Yes. When we asked doctors for clinical trials for the first time, they often declined because they did not believe the drug which was made by Otsuka, a maker of nutritional preparations. But when they found the

> organizer of the clinical trials was Professor Yamamura, they changed their attitude and accepted us. ... Professor Yamamura also asked directly some doctors for cooperation, saying as "Ten [patients] for you." Without this strong leading of Professor Yamamura, it would have taken much more to complete the clinical trials. (Interview)

Pharmacological tests of procaterol with animals started in April 1974, and showed that procaterol was more potent, more selective and longer acting than salbutamol. (Yabuuchi, Yamashita and Tei 1977; Himori and Tira 1977) Clinical trials began in January 1976. Phase I, tests in healthy people, finished in June 1977. Phase II, trials in patients, started in August 1976 and finished in November 1978. Meanwhile, Phase III, which included double blind tests, was conducted from January 1977 to July 1978. Here, again, salbutamol was used in comparison and procaterol was shown to be more potent and longer acting. (Yagura et al. 1979; Shida et al. 1979) This considerable overlapping of different phases of clinical trials was common in Japan at that time. They applied for approval for manufacturing of the drug in December 1978 and this was approved in October 1980. (Nakagawa, interview) Procaterol was marketed in Japan in the same year. This drug was also tested clinically in the US and some other countries, which supported the efficacy and safety of the drug. (Zenetti, Rotman and Dresner 1982; Crowe, Counihan and O'malley 1985; Siegel et al. 1985) A comparative study of procaterol and salbutamol did not identify difference in potency and safety between the two (Crowe, Counihan and O'malley 1985), whereas another study supported that procaterol was longer acting (8 hours). (Siegel et al. 1985)

After its launch the marketing staff of Otsuka had the problem of differentiating procaterol from existing β-stimulants. Shinya Tashiro explained the strategies for its promotion:

> In the early marketing, making the characteristics of the drug clear was essential. We regarded salbutamol as a main rival, because it was at the time the best selling β-stimulant in Japan. First, we emphasized the higher selectivity of procaterol. We said that the drug was more $beta_2$ selective and had fewer effects on the heart than existing others. Second, it was longer acting. Because asthma fits often occur at rising in the morning, they will be avoided if the duration of action is long enough. Another point was that the

> drug was said to have an anti-allergy activity. I heard that this was the first β-stimulant which had such activity. Then, Professor Kazuhiko Ito at Nagoya University suggested that this was the first one of the third generation β-stimulants, whereas isoprenaline belonged to the first generation and salbutamol belonged to the second generation. This was the strongest help in the marketing. (Tashiro, interview)

Kazuhiko Ito at Nagoya University classified β-stimulants into three generations. The first-generation drugs, including isoprenaline, were short acting and not $beta_2$ selective. The second-generation drugs such as salbutamol were more $beta_2$ selective and longer acting. The third-generation drugs, in which procaterol was included, had the strongest $beta_2$ selectivity and the longest duration of action of the three generations (eight hours or longer). (Kawai, Kawakatsu and Takeyama 1987) This classification made salbutamol in the second generation sound obsolete in comparison with procaterol in the third generation.

Another aspect of the post-marketing promotion of procaterol was the development of a variety of administration forms. They marketed smaller tablets, granules and syrup of the drug mainly for younger patients in October 1982. (Shiota et al 1981; Baba et al. 1981) They also added aerosol, aerosol for children and inhalation solution of procaterol in June 1987. (Hamada et al. 1986; Mikawa et al. 1986) As a result, procaterol had the largest variety of preparations in β-stimulants available in Japan. This was important because the variety of asthma patients is also high: from babies to old people. Variety of preparation gives doctors flexibility of treatment. Therefore, Japanese practitioners welcomed the rich variety of procaterol, according to Tashiro. (Tashiro, interview) This development of additional forms of procaterol also helped to maintain the sales of the drug. (Miwa, interview) In Japan, the government have regularly revised prices of drugs and the prices in general have been gradually decreasing. (Campbell and Ikegami 1998, p.158) The price of procaterol also has decreased up to almost half of the original price of nineteen years ago. The drug had sales of more than 13 billion yen in 1998, but they consisted of 3.9 billion yen sales of its tablets, 1.7 billion yen of its mini tablets, 2.7 billion yen of syrup, 4.4 billion yen of its aerosol, and so on. (Tashiro, interview)

In fact, procaterol was such a success in the Japanese market that it outsold salbutamol, the best selling β-stimulant in the world. The sales of salbutamol in Japan were about 40 % of those of procaterol. (GlaxoWellcome (Japan), internal documents) Two reasons for this have already been mentioned. First, procaterol was more potent and longer acting that salbutamol. Second, procaterol had a variety of forms. It should be noticed that both doctors and patients traditionally preferred oral medicines to inhaled medicines in Japan. Both were accustomed to the former. In addition, the latter needed a doctor's instruction to patients about how to use inhalers. Doctors were unwilling to do this under the notoriously busy situation described as 'three minute consultation,' according to Mike Nakayama, the product manager at GlaxoWellcome (Japan).[4] Third, in European countries and the United States, doctors preferred salbutamol because its efficacy and safety were recognized through its long-term use and because it was cheaper. On the contrary, under the traditional health care system in Japan, doctors tended to prefer new drugs because they benefited doctors and hospitals from a bigger gap between the reimbursement price and the real price they paid and because they were usually better than older ones. Finally, Glaxo in Japan, strategically, did not put stress on the marketing of salbutamol, because its market size was relatively modest compared with other products of the company. Even in the respiratory drug area, the company put more stress on inhaled steroids. (Nakayama interview) Salmeterol has not yet been sold in Japan at present.

4.7. Discussion

4.7.1. Normal-scientific Discovery and Reverse Salient

Compared with the discovery of propranolol discussed in the previous chapter, the discovery of salbutamol and that of inhaled BDP can be regarded as a normal-scientific discovery rather than a paradigmatic discovery. Isoprenaline, a non-selective β-stimulant which had actually been used as a bronchodilator, and prednisolone and other glucocorticoids which had actually been used for the

[4] This interview with Mr Mike Nakayama was conducted on 24 March 2000.

treatment of asthma, were already in use. Neither discovery contradicted any existing major theory. Major problems in research on them were clear: enhancement of the potency, improvement of the selectivity, and extension of the duration of activity.

Selectivity in β-stimulants and glucocorticoids is very important because this leads to reduction in side effects. Beta stimulants mimic adrenaline and glucocorticoids mimic cortisol. Both adrenaline receptors and glucocorticoid receptors are widely distributed in the body. Non-selective or poorly selective drugs will act on all receptors of the same kind in the body and cause various responses of the body. This is one of the major causes of side effects of these drugs. In the case of glucocorticoids, in addition, some of them significantly act on mineralocorticoid receptors as well. Duration of activity is also very important, because patients cannot have a sound sleep and wake up feeling good if duration of activity is not long enough. In particular, asthma tends to worsen during the night and its morning fits may be fatal.

Research on anti-asthmatic drugs at Glaxo headed for these specific problems in existing drugs. Isoprenaline, the commonly used β-stimulant before salbutamol, lacked bronchial selectivity and was short acting. Prednisolone, the commonly used glucocorticoid before BDP, was also lacking selectivity and was only orally effective. Its use for asthmatic treatment, therefore, caused considerable systemic effects. Thus, lack of the selectivity and shortage of the duration can be regarded as the "reverse salients" of β-stimulants. A reverse salient in technological change is a component in the technological system that has fallen behind or is out of phase with the others, according to Thomas Hughes, the proponent of the notion. Scientists and engineers concentrate on the correction of reverse salients. When a reverse salient cannot be corrected within the context of an existing system, the problem becomes a radical one, the solution of which may bring a new and competing system. (Hughes 1987, p.73-75; Hughes 1983, p. 79) Occurrence of systemic side effects was the reverse salient of glucocorticoids for asthmatic treatment. In addition, β-stimulants and glucocorticoids deal with different causes of asthma. The former works by dilation of the bronchial muscle. The latter is involved in control of inflammation of mucosa

inside the airways. When we regard the asthma therapy as a technological system, the progress in β-stimulants possibly causes reverse salients in glucocorticoids. These reverse salients were obvious for researchers at Glaxo, who were working on this therapeutic area. They could easily turn the reverse salients into critical problems (Hughes 1983, p. 80), though this does not mean that their solution was easy.

Researchers at Glaxo, eventually, coped with those critical problems, as we can see in the case studies. They first tried to find a longer acting β-stimulant and, as a result, they found salbutamol, which is not only longer acting but also, unexpectedly, bronchi selective. Then, they turned their attention to glucocorticoids, because another cause of asthma had to be controlled. They solved the problem of selectivity by using an existing topical glucocorticoid, BDP, by inhalation, not by discovering a selective glucocorticoid. This solution is justified by a view that the site-specific delivery is important because all cells probably have the same glucocorticoid receptors. (Taylor and Shaw 1993; Utiger 1993) This was more than the modification of an existing drug in the same approach. This was innovative in finding a new approach to the use of glucocorticoids for asthma and also in finding a new application of topical glucocorticoids. After the development of BDP inhaler, they turned their attention to β-stimulants again. The reverse salient this time was also extension of duration. Salbutamol, after all, did not get rid of the reverse salient completely. More than 8 hours long duration was necessary. What is important here is that this reverse salient became critical because rival companies had developed longer acting β-stimulants such as procaterol. Here, it is obvious that reverse salient is not only a technical phenomenon but also a social one. In the area of glucocorticoids, Glaxo continued to search for a safer steroid. As a result, they found fluticasone propionate, which is claimed to be safer because it is orally inactive. Thus, these drugs can be seen as a result of Glaxo's struggle with the reverse salients. The motive of this struggle can be seen in Jack's words:

> **Jack**: I asked myself. What is wrong with salbutamol? Answer: nothing except that it is too short active. Then, I was trying to make a longer acting one. It's simple. Similarly, that is why I chose fluticasone propionate. Because I perceived the patents on beclomethasone dipropionate disappear, what would we do? What do we need? What is wrong with beclomethasone

dipropionate? It was not selectively acting. We should make more selectively acting, something better. That is fluticasone. So, why? What made me think of this was, in one word, necessity. I had to. It was necessary.
Hara: Necessary from the medical reason?
Jack: Medical, but double, in order to keep my organization solvent. So, never mind the medical, but by the way, the only way to keep it solvent is to satisfy the medical problem. (Interview)

Thus, the normal-scientific discovery of drugs seems to be conducted as the correction of reverse salients within the context of an existing system, if we adopt Hughes' terminology. Once a reverse salient is corrected, another will appear. As a result, a series of discoveries, such as salbutamol, BDP inhaler, salmeterol and fluticasone propionate, emerge. Evolutionary economists would describe this as a technological trajectory. (Dosi 1982; Nelson and Winter 1977) These characteristics seem to be consistent with Kuhn's analogy, normal science as puzzle-solving. (Kuhn 1970, pp.35-42) However, the case of BDP inhaler was somewhat different from the other cases in adopting a different "rule" (Kuhn 1970, pp.38-39), that is to say, a combination of topical steroids as compounds and inhalation as the way of administration.

4.7.2. Social Process in the Shaping of Drugs

In the cases of anti-asthmatic drugs, as in other cases, the process of discovery and development involved considerable uncertainty. Mechanisms of interaction of a drug and the body were so complex that researchers did not understand them fully. As a result of this uncertainty, there were scientific controversies: for example, whether or not beta-adrenergic receptors are desensitised by long time exposure to β-stimulants; whether or not the regular use of β-stimulants increases asthma mortality; and whether or not socio-economic factors such as financial barriers to primary care was a major cause of the "epidemic" of asthma mortality in New Zealand. The market for drugs also has uncertainty. In the case of procaterol, this uncertainty raised some problems: for example, which is better, a very effective drug with some but tolerable side effects or a less effective drug with fewer side effects? These controversies and problems were not solved by examining nature alone. It was social process that solved them. Sometimes, powerful leadership brought a closure. When David Jack

began the search for a longer acting β-stimulant, he did not persuade doubtful fellow researchers but told them to do it. When Otsuka's staff discussed the choice of drug for development, it was the voice of Akihiko Otsuka that was crucial. On the other hand, a subtler, longer lasting process toward a closure occurred when there was no single powerful authority. The β-stimulant controversy has been virtually closed partly because the "epidemic" of asthma mortality waned, partly because there was a consensus that the combination of β-stimulants and glucocorticoids should be adopted in the management of asthma from the therapeutic point of view, and partly because the safety of long-acting β-stimulants such as salmeterol became widely accepted as they were clinically used for quite a long time. Thus, the wane of interests, the emergence of a practical consensus, induction by test and induction by use collectively brought a closure to the controversy. It should be noted that the properties of β-stimulants were not truly known by these. (Cf. MacKenzie 1996, pp.257-258)

4.7.3. Substances in the Shaping of Drugs

In the previous chapter, we discussed the role of theories and that of substance in pharmaceutical innovation. The provisional conclusion was that it is impossible to determine which comes first, a theory or a substance. The cases in this chapter support this conclusion. The research that produced salbutamol in 1966 was based on the receptor theory, for example. However, the researchers did not know the concept of subtypes of β-receptors, which were published in 1967 by Lands and his colleagues. (Lands et al. 1967) Salbutamol, later found to be a $beta_2$ selective stimulant, supported Lands' theory. David Jack, in my interview, mentioned his three gurus. Two of them were human: R.P. Stephenson and D.E. Koshland, Jr., both of whom contributed to progress of receptor theory. (Stephenson 1956: Strange and Koshland 1976) However, the third guru Jack mentioned was non-human: salbutamol. This raises an important question: can people learn from substances? Salbutamol, of course, does not speak. Mediated by social processes, the properties of salbutamol were measured, interpreted and understood. However, salbutamol is, of course, not purely socially constructed. Salbutamol has something imperative

within it, something foreign to human society within it. Because of this, researchers can learn something from substances, given the existence of society which provides them with theories, equipment, salaries and so on.

4.7.4. Making Differences

Because procaterol was a product of the normal-scientific discovery, there were some similar drugs when it was developed. Therefore, it was necessary for Otsuka staff to make its differences from the others clear in order to sell it successfully. The differences had to be conceptually expressed and empirically demonstrated. Kazuhiko Ito's classification of β-stimulants generations was especially helpful in the marketing, because it made existing drugs sound obsolete. Results of comparative clinical trials were fully made use of in the marketing. These are understandable because a normal-scientific discovery has, by definition, at least an exemplar and maybe some similar discoveries, whereas a paradigmatic discovery has no exemplar and must be distinguishable. Therefore, the efforts to point up differences from other drugs are probably more critical in the development and marketing of drugs coming from normal-scientific discoveries than in those from paradigmatic ones. Thus, when we look not only at discovery but also at development and marketing, we may also be able to identify different types of innovation in the pharmaceutical industry.

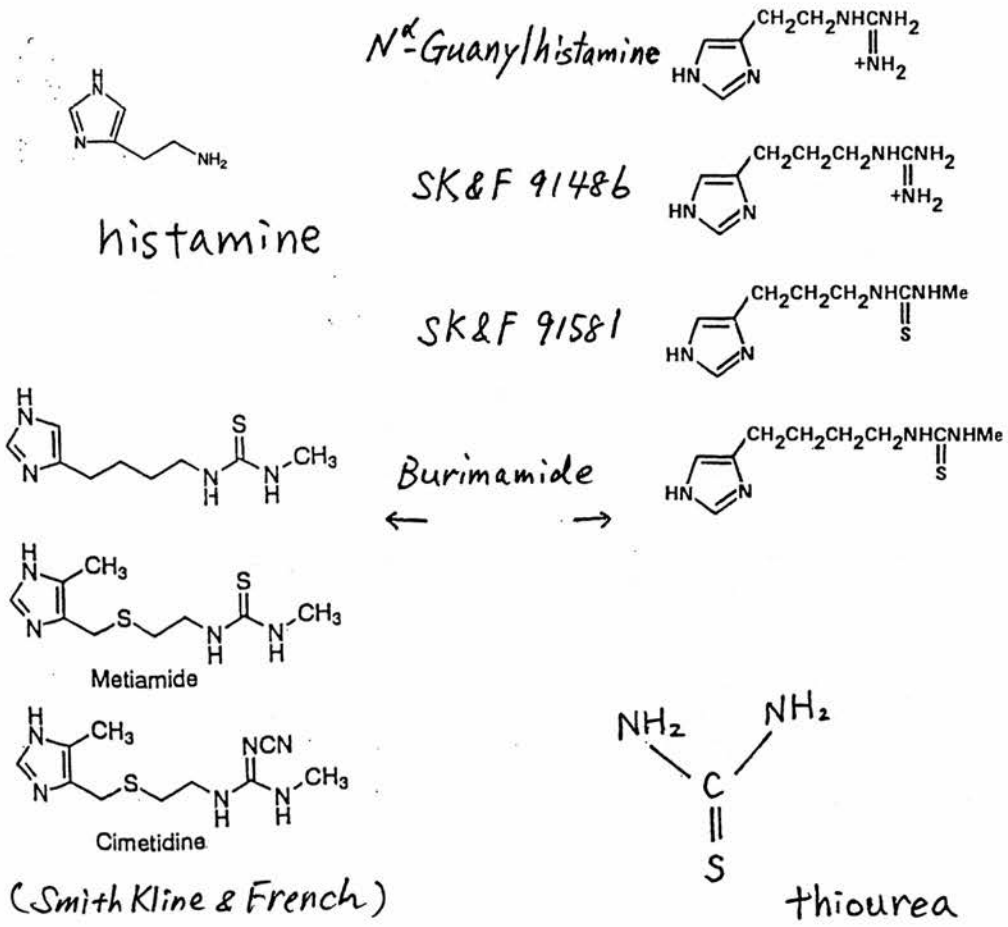
In the next chapter, we examine the cases of H2 antagonists, drugs for the treatment of peptic ulcers. The cases consist of a paradigmatic discovery, cimetidine, and two normal-scientific discoveries, ranitidine and famotidine. We will examine their development and marketing processes as well in order to identify the types of innovation in the pharmaceutical industry.

Chapter 5: Histamine H_2 Antagonists

5.1. Introduction

Histamine H_2 antagonists are a group of drugs which are used for the treatment of peptic (both duodenal and gastric) ulcer. One of the main causes of peptic ulcer is believed to be an excessive secretion of acid in the stomach, due to various factors such as stress and doses of aspirin. (Another main cause is now believed to be *Helicobacter pylori*, a kind of bacteria discovered in 1983, which destroys the mucous membrane of the stomach). Unlike previous drugs which just neutralised the gastric acid, histamine H_2 antagonists reduce dramatically the amount of acid secreted in the stomach. Histamine H_2 antagonists inhibit histamine, one of the important chemical transmitters in the body, from fitting into the receptors called histamine H_2 receptors, which play an essential role in the acid secretion in the stomach. Histamine H_2 antagonists were discovered by (Sir) James Black and his colleagues at the British subsidiary of SmithKline and French (now SmithKline and Beecham) in the early 1970s. Though the first marketed histamine H_2 antagonist was cimetidine (Tagamet®) made by SmithKline and French, it had two precursors called burimamide and metiamide, both of which were also discovered in the same company by Black and colleagues. The second histamine H_2 antagonist to be marketed was ranitidine (Zantac®) discovered by (Sir) David Jack and his colleagues at Glaxo (now GlaxoWellcome). And the third was famotidine (Gaster®, Pepcid®) discovered by Isao Yanagisawa and his colleagues at Yamanouchi in Japan. These histamine H_2 antagonists brought a major breakthrough to the area. First, therapeutically, they have eliminated the need for surgery for the treatment of peptic ulcer. The disease has been increasingly treated by physicians rather than by surgeons since the advent of these drugs. Second, they were extremely successful in the market. Cimetidine and ranitidine were two of the top-selling drugs in the world, and famotidine was one of the top-selling drugs in Japan and also considerably successful in other countries. Each of them has provided each company with enormous profit and contributed to the company's further investment in R&D and other operations. In this chapter, we look at these histamine H_2 antagonists.

Figure 5.1: The Compounds Discussed in This Chapter



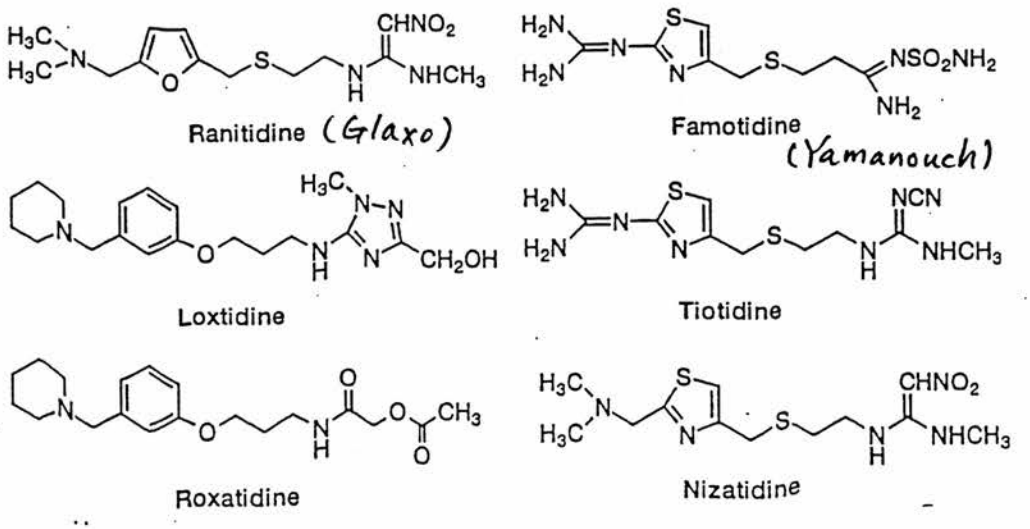


Table 5.1: Major Events Discussed in This Chapter

Year	SmithKline and French	Glaxo	Yamanouchi
1964	Research start		
1968		Antigastrin research start	
1970	Burimamide discovery		
1971	Metiamide discovery		
1972	Burimamide report Cimetidine discovery	H_2 antagonists research start	
1976	Cimetidine launch	Ranitidine discovery	Research start
1980			Famotidine discovery
1981		Ranitidine launch	
1985			Famotidine launch

5.2. Burimamide to Cimetidine

5.2.1. Introduction

James Black applied the same approach to the discovery of histamine H_2 antagonists as to his discovery of β-blockers, that is, he started from a natural occurring molecule, and then modified its structure to enhance the selectivity and stability to a particular type of receptors. The natural molecule this time was histamine, whilst for β-blockers it was adrenaline. Although the idea was quite simple, its realization was not at all easy. It took Black and his colleagues six years to discover the first H_2 antagonist, burimamide, in 1970. However, burimamide had a decisive flaw which prevented its practical use as a drug. They modified it and discovered metiamide in 1971. Though metiamide was free from the problem which burimamide had, it had undesirable side effects. They modified it further and eventually succeeded in the synthesis of cimetidine in 1972. Cimetidine finished clinical trials successfully and was marketed in the UK in 1976 and in the US in 1977. (Duncan and Parsons 1980) In the early 1980s, it became the top-selling drug in the world. (Ganellin 1985, p.115)

5.2.2. Discovery of the Histamine H_2 Antagonist

For a long time, the relationships between histamine, gastrin and gastric secretion were poorly understood. Gastrin as the gastric secretion stimulant was first reported by J.S. Edkins in 1906, when he derived it from an extract of the stomach. (Edkins 1906) Histamine was discovered by H. Dale and P.P. Laidlaw in 1910. (Dale and Laidlaw 1910; Sneader 1985, pp.165-166) Gastric secretion stimulants were found in many kinds of extracts of other tissues later. (Koch, Luckhardt and Keeton 1920; Ivy 1930) Because at that time it was known that histamine stimulates acid secretion (Koch, Luckhardt and Keeton 1920; Popielski 1920) and it exists in many tissues (Abel and Kubota 1919), some researchers concluded that histamine and gastrin were identical. (Rothlin and Gundlach 1921; Sacks, Ivy, Burgess and Vandolah 1932; Gavin, McHenry and Wilson 1933) However, in the mid 1930s, researchers at McGill University, Canada, claimed that gastrin and histamine were different substances. (Babkin 1934; Komarov 1938; McIntosh 1938) S.A. Komarov repeated the Edkins' experiment more systematically and showed that even histamine-free extract of the stomach could cause the secretion of gastric acid whereas histamine-free extracts of other tissues could not. (Komarov 1938) Moreover, F.C. McIntosh compared the increase of histamine caused by injection of histamine with that caused by stimulation of the vagus nerve, the widely distributed nerve, and suggested that histamine functioned as a "local hormone" working indirectly for the acid secretion rather than as a "true hormone" (that should have been "gastrin") working directly. (McIntosh 1938) Thus, they showed that gastrin was different from histamine and suggested that gastrin might work more directly in the gastric secretion and be more important than histamine. Since then, many efforts had been made to unveil the new hormone, gastrin. (E.g. Uvnäs 1943; Harper 1946; Jorpes, Jalling and Mutt 1952) However, the controversy continued until gastrin was identified chemically. For example, C. F. Code discussed on gastrin as below:

> "Gastrin" then, may be simply another histamine releaser. Study of whether this action is confined to the release of histamine in the gastric mucosa or whether it is shared by other tissues is hampered by the lack of a ready source

> of purified "gastrin" and, apparently, by the difficulty of preparing it so that it will be free of histamine. (Code 1956)

At last, in 1964 gastrin was isolated (Gregory and Tracy 1964) and its chemical structure, a polypeptide hormone, was identified subsequently. (Gregory, et al. 1964) Then, "[m]any researchers turned their attention to seeking specific inhibitors of gastrin-induced acid secretion". (Ganellin 1982, p.4)[1] This was represented by the statement below about gastric secretion in a physiology textbook published in 1968:

> Histamine and gastrin deserve some special consideration, histamine because it has for such a long time been involved in theories of gastric secretion as well as other activities, and gastrin because it is now firmly established as playing a major role in gastric activity and also is the first gastrointestinal hormone whose chemical nature has been determined.
>
> .....
>
> The role of histamine as a physiological agent in gastric secretion can still not be regarded as either proved or disproved. (Davson and Eggleton eds. 1968, p.619)

Similarly, L.R. Johnson in his paper in 1971, "Control of Gastric Secretion: No Room for Histamine?" argued that "histamine may have nothing to do with the direct stimulation of acid secretion". (Johnson 1971)

This view was reinforced by the fact that existing antihistamine drugs at the time could not stop acid secretion (Ganellin 1982, pp.2-3; Patrick 1995, p.283; Sneader 1985, p.170),[2] though they could stop other body responses caused by histamine, particularly allergic symptoms like urticaria and hay fever. (Sneader 1985, pp.167-168; Ganellin 1982, p. 2) In addition, in the 1950s M. I. Glossman and his colleagues at University of Illinois College of Medicine, supported by Eli Lilly, examined gastric acid-secretion inhibitory activity of various histamine analogues, but no effective inhibitor was discovered. (Glossman, Robertson and Rosiere 1952; Ganellin 1985, pp.99-100) Therefore, the idea of using histamine antagonists as the way of inhibiting acid secretion was generally regarded as "played out." (Ganellin 1982, p.4)

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[1] However, there seemed to exist some researchers who kept believing that histamine was significant in the gastric secretion. (E.g. Code 1965)

[2] There was also a concerted effort by researchers at Eli Lilly in the 1950s to find an antagonist of histamine-stimulated acid secretion. (Ganellin 1982, p.4)

For example, when Glaxo started its research programme for anti-acid drugs in 1968, they first did it by searching for an anti-gastrin compound.[3]
James Black described the atmosphere at the time:

> ... suddenly, [in 1938], we had the discovery of gastrin. Everybody went alive. And they were able to show its structure and they synthesised it. ... we now have up until 1938 everybody saying histamine, after 1938 everybody saying gastrin. So when the anti-histamine drug didn't stop acid secretion, it was said that that was because acid was stimulated by gastrin. Now that is why no one was looking for a histamine antagonist because they didn't think histamine was involved. (Interview)[4]

Why then did Black follow a different way? Two reasons have been put forward. One is his experience of adrenaline receptors. Black had succeeded in finding beta-adrenergic receptor antagonists before joining SmithKline and French. (See Chapter 3) His familiarity with two types of adrenaline receptors led him to the analogy of the histamine receptors. (Duncan and Parsons 1980, 620; Black interview) The other is previous research on histamine by other scientists. Conventional antihistamines failed not only to inhibit the acid secretion in the stomach but also to block the dilation of blood vessels and some other actions caused by histamine. Therefore, in 1948, B. Folkow, K. Heager and G. Kahlson speculated that there might be two types of receptors sensitive to histamine. (Folkow, Heager and Kahlson 1948)[5] These two reasons led Black, the newly appointed Head of Biological Research of the British laboratories of SmithKline and French (UK), to propose a research programme on the unidentified second histamine receptor in 1964. (Duncan and Parsons 1980, 620)

The research programme began in September 1964 with the expectation that it would be over by Christmas. It consisted of Black and M.E. Parsons as pharmacologists, W.A.M. Duncan as a biochemist and G. J. Durant as a chemist. As they found the

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[3] Interviews with Sir David Jack and with Ms Angela Palmer. See footnote 13.
[4] This interview with Sir James Black was conducted on 3rd March 1999.
[5] Later, but before the SmithKline and French team identify the histamine H_2 antagonist, Ash and Schild proposed in 1966 that the actions of histamine blocked by conventional antihistamine drugs should be defined as histamine H_1 receptors and that other actions not blocked by the antihistamines should be mediated by other receptors, or non-H_1 receptors, with results of further investigations on the actions of histamine by their own and others. (Ash and Schild 1966; Ganellin 1982, pp.2-3; Duncan and Parsons 1980, 620)

programme unexpectedly difficult, J.C. Emmett and C.R. Ganellin joined in the team in 1965 and 1966 respectively (Duncan and Parsons 1980), in order to reinforce the chemistry part.

Because there was only a hypothesis, they started to modify histamine itself. Many different approaches were tried, including a straightforward analogy with β-blockers, to fuse a benzene ring and an imidazole ring together. But all of these early trials did not work. (Ganellin 1982, pp.5-6) Numerous failures raised doubts about the hypothesis. Only the results that showed the different stimulating effect on the different receptor sites between 2-methylhistamine and 4-methylhistamine, implicating the two types of receptors, encouraged them to continue. However, this did not lead to the discovery of selective antagonists. (Ganellin 1982, p.7) In the first four years, about 200 compounds were synthesised and tested with no success. Meanwhile, Parsons found that the assay they had been using was not able to detect partial agonists. Partial agonists are the compounds which have both characteristics as agonists and antagonists. He suggested a new assay able to find even partial agonists. (Duncan and Parsons 1980) They re-examined some of the compounds synthesised earlier, which had some potential from the theoretical point of view. (Ganellin 1982, p.7) By this screening, they found one compound showing a weak blocking activity. This had been synthesised by Durant in 1964, the very first year of the research programme! (Duncan and Parsons 1980)[6] It was not detected in the first screening because it was a partial agonist. The compound, N^{α}- guanylhistamine (SK&F 71448) became the lead compound for the next stage. (Ganellin 1982; Duncan and Parsons 1980)

Before they discovered N^{α}- guanylhistamine, they had also found a compound[7] which inhibited the acid secretion. However, its activity was not by antagonism at the histamine H_2 receptors but by another mechanism. There was strong pressure both within the research team and from the company to develop it, and eventually some diverted effort along this track was made temporarily. However, Black succeeded in

[6] Historically, this compound was first synthesised in 1928, but was reported to be devoid of interesting physiological activity. (Ganellin 1985, p.102)

[7] α -methyl histidine 3,4-dichlorobenzene sulphonate

reminding the team members that they were not interesting in an antisecretory compound *per se*, but in a competitive non-H_1 receptor antagonist. (Duncan and Parsons 1980) Black put it:

> I was looking for a histamine antagonist. I was not looking for something which would inhibit acid secretion. ... This particular compound inhibited acid secretion. And then I was put under the great pressures to develop this as an anti-acid secretory compound. And I was able to show that it was the salt of dichlorobenzene sulphonate which was doing the inhibition, and there is nothing to do with histamine at all. And so, "Go away! Don't follow this." (Interview)

Black's reputation was important for the survival of the project. He himself observed:

> [The company] would have to have really good reasons, if you understand, for cutting me off. But they had a problem. Because I had by this time, what you might call, a track record. (Interview)

After the discovery of N^{α}- guanylhistamine, the research team made many of its analogues. One of them, SK&F 91486, which was synthesised in 1968, had a longer side chain and showed a stronger antagonist action though it was still a partial agonist. This made the research team more confident. (Duncan and Parsons 1980)

The organisational pressure, however, increased more and more. The 1967 annual report of SmithKline and French announced that they " began to concentrate [their] efforts on a smaller number of research areas and to give these areas more intensive study." (SmithKline and French, *Annual Report* 1967, p.7) Several research programmes in progress were mentioned there but Black's project was not. Duncan and Parsons described the situation very well:

> The parent company in the United States had had a major reorganisation of its research activities, and questions were being raised about the relevance of the research program in the British laboratories. This probing led to the resolve by the British workers that the survival of the U. K. Research Institute within the SK&F organisation required that it make a major discovery and that it should do it soon. Duncan was now Research Director

> and it was decided that of the various research programs being worked on in Welwyn, the histamine-receptor antagonist program was the one most likely to fulfill this requirement and therefore, that we should concentrate all our available resources on making it happen. This inevitably produced trauma within the Research Institute, and it is very considerably to the credit of all our colleagues that they cooperated in this policy even though it inevitably led to the contraction, or annihilation, of their own favorite programs. These were not happy time... (Duncan and Parsons 1980, 621)

The UK research team invented the term "H_2", in order to emphasise the difference of their objectives from those of their counterpart in the United States and of other companies which were looking for anti-secretory compounds. (Duncan and Parsons 1980, 621-622)[8] It can be said they set their domain not in the specific disease but in the specific approach, at least partly because of organisational reasons as regards their relationship with the US parent company.

In 1969, SK&F 91581, a thiourea analogue of SK&F 91486, was found not to act as a partial agonist, even though its activity as an antagonist was weaker than SK&F 91486. Further lengthening of the side chain of SK&F 91581 led to the discovery in 1970 of burimamide, which showed much stronger antagonist activity without stimulant activity. In total, about 700 compounds had been synthesised and tested before this discovery. (Duncan and Parsons 1980, 622; Ganellin 1982, pp.14-16)[9]

Burimamide demonstrated that there are histamine H_2 receptors and particular compounds that can antagonise the activity of the receptors. Confidence and morale in the research team became very high. (Duncan and Parsons 1980, 622) However, burimamide was not active enough to be given orally. This meant that it could not be considered as a drug candidate. (Ganellin 1982, p.16) Further modification was necessary to find a practical candidate, but Black and Duncan decided that they should undertake single-dose experiments of burimamide in humans to confirm the transferability of the animal pharmacology to humans and that they should publish

[8] Black did not like "H_2" very much as the name of the receptor. In fact, there were people who read the title of the SK&F team's first paper as a new "hydrogen receptor" antagonist! (Black personal communication, October 1999)

[9] About the chemical modification from histamine to burimamide, see Ganellin (1985, pp.102-106) and Patrick (1995).

their data as early as possible. (Duncan and Parsons 1980, 622) The experiments were conducted in 1971[10] and confirmed that burimamide inhibited acid secretion in humans as well as in animals. These findings were very important because they showed a key role of histamine in the gastric secretion which had been controversial for a long time. The results were published in *Nature* in 1972, only a year after the Johnson's "No Room for Histamine" paper. According to Duncan and Parsons (1980), this very early publication came from the intention to encourage other scientists to confirm their findings and to extend the research in the area. It can be imagined that this also affected the valuation of this research by the management of the parent company.

After the discovery of burimamide, various modifications were examined systematically to increase potency. Based on an elegant, rational thinking of chemistry, sulphur was introduced in the side chain by Ganellin. (Black personal communication, October 1999) This, together with the introduction of CH_3 in the ring system, made the compound about ten times more potent. This compound was synthesised in 1971 and named metiamide. (Black et al. 1974; Ganellin 1982, pp.16-23; Ganellin 1985, pp. 106-111; Duncan and Parsons 1980, 623; Patrick 1995, pp.294-298) Because it was effective even by oral administration, they believed that they had at last achieved their objective, a drug! Top priority was given to scaling-up of the synthesis. The team was now expanded and about 150 scientists came to be involved in metiamide and other aspects of H_2 receptors. In March 1972, Duncan, Black and one of their American colleagues visited the Food and Drug Administration (FDA) in the United States to talk about burimamide and metiamide, which was the first of several meetings between SK&F and the FDA on the matter. In June 1972, an application was made to the Committee on Safety of Medicines (CSM) in the UK for a clinical trials certificate for metiamide and this was granted in April 1973. (Duncan and Parsons 1980, 623) The first international symposium on histamine H_2 receptor antagonist was held in London in October 1973.[11]

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[10] The first volunteers were Duncan and Ganellin. (Duncan and Parsons 1980, 622)

[11] In the welcome speech in the symposium, Duncan stated that in the drug industry potential new drugs were usually not discussed at such an early stage, that for various reasons nevertheless he decided the early disclosure of data and that one of the reasons was to improve its development.

However, metiamide was not free from flaws. Even as early as March 1972, the research team regarded the presence of a thiourea group in the molecule as a potential disadvantage and started an effort to replace it with another structure. The pre-clinical development found that metiamide produced a granulocytopenia, a shortage of the normal number of granular leucocytes in the blood, in some dogs, and some other side effects in rats and dogs. These effects were judged to be acceptable therapeutically when both merits and demerits of metiamide were taken into account. (Duncan and Parsons 1980, 623) However, of 700 patients treated with metiamide in the clinical trials, a few cases of granulocytopenia were reported. (Ganellin 1982, p.23) Because of these, the CSM recommended the suspension of the UK clinical trial certificates in June 1974. The FDA also took a similar action. The company had some meetings with the FDA and the CSM. In the UK the clinical trial certificate for metiamide was re-granted but for use only in seriously ill patients. (Duncan and Parsons 1980, 624) Duncan and Parsons described how this matter, together with Black's resignation in 1973 to accept the chair of pharmacology at University College, London, depressed the research team. (Duncan and Parsons 1980, 624) They had already started work on modifying the structure of metiamide in March 1972, and eventually found that its nitroguanidine analogue and cyanoguanidine analogue were as potent as metiamide even without the thiourea group, which was regarded as the cause of the side effects of metiamide. The cyanoguanidine analogue was more potent and chosen as a successor of metiamide. This is cimetidine (Brimbelcombe, et al. 1975; Ganellin 1981; Ganellin 1982, pp.23-27; Ganellin 1985, pp.111-114; Patrick 1995, p.281), which was synthesised in 1972. (Ganellin 1982, p.33) It gradually became clear that cimetidine did not have the major side effect of metiamide. In 1974, cimetidine was administrated to a patient who had agranulocytosis, serious granulocytopenia, caused by metiamide. The substitution of cimetidine for metiamide led to a rapid recovery from agranulocytosis. This was evidence that cimetidine is free from this side effect. (Duncan and Parsons 1980, 624) After that, the development of cimetidine progressed rapidly. The drug was first

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(Duncan 1973) But, again, the symposium was also regarded as held at least partly because of the politics in the organisation, academic and medical society. The social role of these kinds of symposia in medical sciences is discussed by (Thagard 1999, pp.91-92, pp.185-198)

marketed in the UK in 1976, in the US in 1977 and in over 100 countries by 1979 under the trademark Tagamet. (Ganellin 1982, p.33)

SmithKline and French intensively promoted cimetidine worldwide. In the statement of the chief executive officer in the 1976 annual report, the then chairman, Robert Dee, stated, "[w]e will devote a major share of our resources ---people and money--- to make 'Tagamet' available to patients throughout the world in 1977. ... The effective worldwide marketing of 'Tagamet' is a top priority." (SmithKline Corporation, *Annual Report* 1976, p.3) The most important thing was to inform the medical market about the drug. They held the Second International Symposium on Histamine H_2-Receptor Antagonists in London in October 1976. (SmithKline Corporation, *Annual Report* 1976, p.9) Face-to-face promotion was also conducted. The following extract from the 1976 annual report shows it:

> Because of the uniqueness of the H2-Antagonist concept, our sales representatives will be informing the world's physicians of a new method of treating gastrointestinal disorders. To prepare our people to do this, we have developed an intensive and comprehensive instruction program. The program includes training in the safety and efficacy profile of the compound, and also instruction in the concept of biochemical receptors and antagonists, which underlies the mode of action of 'Tagamet.' (SmithKline Corporation, *Annual Report* 1976, p.9)

The following extract from the 1977 Annual Report of SmithKline Corporation shows how the company prepared the worldwide market introduction of cimetidine:

> ... parallel strategic programs were implemented to assure that we had adequate chemical supplies and pharmaceutical production facilities, and the marketing capability to introduce the product effectively to the medical professions. Production facilities were expanded in the United Kingdom, Germany, France, Puerto Rico and a number of other countries. Sales forces were increased in several international markets, including Spain, Germany and Italy. (SmithKline Corporation, *Annual Report* 1977, p.4)

The development from histamine, through burimamide and metiamide, to cimetidine has been regarded as one of the best examples of "the rational approach" (Sneader 1985, p.171; Patrick 1995, 281) of drug discovery. This also has changed the view of

the role of histamine in the gastric secretion. It can be seen clearly when we compare the following statement in a recent textbook with that in 1968 cited above:

> Histamine is a major physiological mediator of HCl secretion. Cimetidine, a specific antagonist of H_2 receptors, blocks a large portion of acid secretion elicited by any known secretagogue. ... Gastrin is not as potent a direct stimulant of parietal cells as acetylcholine or histamine. The physiological response to elevated levels of gastrin in the blood is greatly attenuated by cimetidine. Thus a major component of the physiological response to gastrin may result from gastrin-stimulated release of histamine. (Berne and Levy eds. 1996. pp.466-467)

Black won a Nobel Prize in 1988 for his achievement in the discoveries of β-blockers and histamine H_2 antagonists.

5.3. Ranitidine

5.3.1. Introduction

In 1968, David Jack, who was then research and development director at Allen and Hanburys, set up a research team for a gastrin antagonist, after he has successfully achieved the discovery of salbutamol and BDP inhaler. (See Chapter 4) The team leaders were Roy Brittain (pharmacology) and Barry Price (chemistry). They changed their target to histamine H_2 antagonists when burimamide appeared. They eventually discovered a new potent H_2 antagonist, ranitidine, in 1976. Ranitidine is a member of a new chemical class of H_2 antagonists in which the imidazole ring in burimamide, metiamide and cimetidine molecules is replaced by a furan ring carrying a basic substituent. Ranitidine was found to be more potent and more selective than cimetidine. Because of these superior characteristics as a drug and Glaxo's intensive global marketing efforts, it steadily displaced cimetidine after it was marketed in 1981 and became the world top selling drug by 1988.

5.3.2. Shaping a World Best Selling Drug

Jack and his colleagues first considered the possibility of an improved treatment for peptic ulcer in 1968. (Jack personal communication, February 2000; Glaxo internal documents) Originally, this research team was directed towards the discovery of an antigastrin compound. (Glaxo internal documents; Jack interview; Palmer interview)[12] This was found to be a very difficult task because gastrin is a relatively large peptide hormone whose cellular receptors were ill-defined. (Jack personal communication) The project was about to be axed after it had been unsuccessful for almost four years. (Palmer interview) In 1972, the research objective was abruptly changed to a new histamine H_2 antagonist when Black's work on histamine H_2 receptors was made public. Jack explained:

> Roy Brittain and I attended a lecture by James Black in Hatfield Polytechnic in which he revealed that burimamide, a simple derivative of histamine, inhibits not only histamine-induced acid secretion in animals and man but also that which follows ingestion of food. These results established beyond doubt the physiological role of histamine in acid secretion and gave our chemists a much easier starting point than gastrin analogues for their project. At that time, large molecules such as gastrin were "bad news" for medicinal chemists because their chemistry and biology were more difficult and less well understood than that of small mediators like histamine. (Interview)

The SmithKline and French researchers probably believed that the imidazole ring, as in histamine or an alternative basic aromatic ring system was essential in a potent histamine H_2 antagonist. This is evident in cimetidine and related compounds in the contents of their patent on H_2 antagonists. (British Patent 1421792) The first objective of the Glaxo research team was, therefore, to find a potent H_2 antagonist that does not contain such a ring system, rather than to find a more selective drug. (Jack interview and personal communication) Their starting point in 1972 was burimamide and later cimetidine. Jack put it:

> By 1976, we were looking for a drug as good as cimetidine. What we found was a better one. Ranitidine proved to be about 5 times more active than

[12] The interview with Sir David Jack was conducted on 27th April 1999. The interview with Dr John Wood and Ms Angela Palmer at GlaxoWellcome was conducted on 9th April 1999.

> cimetidine as a histamine H_2 antagonist and to be more selectively acting because, unlike that drug, it does not inhibit cytochrome P450 processing enzymes in the liver or antagonise the actions of testosterone in man. We were very lucky to achieve this outcome because we were unaware of these shortcomings of cimetidine when ranitidine was first synthesised. (Interview)

The Glaxo team struggled unsuccessfully for nearly four years to circumvent the SK&F patents by replacing the imidazole ring by a variety of non-basic aromatic systems. (Jack personal communication) The breakthrough came in 1976 when John Clithelow, a senior medicinal chemist, having made some poorly active furan analogues of potent H_2 antagonists, remembered that furan can be converted into a tertiary amine by a specific chemical procedure. The resultant compound retains the furan structure but it has a basic group *outside* the furan ring system. (Jack personal communication)

The conversion was first carried out on the furan analogue of metiamide and yielded a modestly potent H_2 antagonist. Next came the dimethylaminomethyl furan analogue of cimetidine. It was found to be less active than cimetidine and to be toxic in animals. After a few modifications were tried in the side chain, the one that contains an unusual nitro-ethene grouping was found to be more active and less toxic than cimetidine. This was synthesised in 1976, named ranitidine. (Jack personal communication; Technical booklet published by Glaxo Group Research titled *Ulcers*, p.12) However, because ranitidine was a poorly soluble solid, it was replaced in the development programme by ranitidine hydrochloride in 1977.[13] Following extensive toxicity tests in animals, clinical trials of ranitidine started in 1978. Its efficacy and safety was confirmed in clinical trials. It was marketed in the UK in 1981, in the US in 1983, under the trademark of "Zantac." (Jack personal communication; Brittain, Jack and Price 1981; Brittain and Jack 1983; Glaxo internal documents; Bradshaw et al. 1979; British Patent 1565966) Further research found that the furan ring system of ranitidine could be replaced by other base-substituted aromatic structure to yield a variety of potent, long-acting H_2-antagonists but none was found to be superior to

[13] For convenience, hereafter I will refer to the compound simply as ranitidine instead of ranitidine hydrochloride.

ranitidine. (Jack personal communication; Brittain and Jack 1983, 74; Brittain, Jack and Price 1981, 311-312; Palmer interview)

Because they could obviously witness the success of cimetidine, it is easy to speculate that Glaxo was less uncertain and more confident about the success of ranitidine, which was gradually found to be better than cimetidine. This led the company to undertake the large investment in manufacturing and marketing. This also led the then quite "Commonwealth" oriented company to become a really international company operating in many countries including other European countries, the United States and Japan. Documents published by the company described the situation:

> All available resources were swung behind the new compound. In the process, Glaxo began to break new ground in almost every department. Clinical trails were wider in scope and completed far more quickly than had ever been the case before. ... Marketing was approached in a totally new way, with co-promotion and licensing deals to achieve rapid penetration of markets. ... At the same time, greater-than-ever investment in production resources helped to meet the demand as it rose. In summary, Zantac was developed and brought to market in a single, worldwide programme, rather than locally and piecemeal as had always been the case in the past. (Glaxo 1987, p.10)

Angela Palmer, who had worked closely with the research team, also described it:

> Ranitidine was first made chemically in 1976. Ranitidine hydrochloride ... was made in mid 1977. And large-scale production in a production plant at Montrose was commenced in October 1980. And certainly, a large amount of effort was put into the development. The company realised it's a good drug at the very early stage. (Interview)

John Wood, who had worked on the clinical trials since 1983, explained the internationalisation as follows:

> We were a small-medium sized Commonwealth-English company. And we had a new product. We wanted to internationalise. Our chairman at the time, Sir Paul Girolami, decided this company needed to be internationalised, so we had to take a new drug, Zantac, and set up new companies in other countries, for example, America. ... Zantac was the opportunity. It was the

> new drug we would take into new countries. Now, I think that if we hadn't had Zantac, [we] might have been less encouraged to move other countries. (Interview)

In the course of this all-out and worldwide development of the drug, the approach that was taken was so-called "development-in-parallel." This approach was based on the idea that every month lost between synthesis and sales was potential revenue lost. (Glaxo 1987, p.11) This represents their confidence in the success of the drug in the market. Roy Brittain, the research director at Ware since 1983, stated, "Had we done our test strictly one after the other we could have lost a year or more in development time." (Glaxo 1987, p.11)

Richard Blythe, the secondary production controller at Glaxo Pharmaceuticals stated:

> We got going on production facilities before the clinical trails or even the animal trials were finished. If you wait until trials are over, you're eating all the time into your patent life. (Glaxo 1987, p.11)

The significance of communications between functions was emphasised. John Padfield, the then pharmacy director at Glaxo Group Research, put it:

> We had to understand what was going on in development, of course. We had to talk constantly with the marketing people to discover what they wanted in terms of presentation, dosage forms, likely shelf lives and so on. We also had to understand the needs of the production people. (Glaxo 1987, p.12)

All these efforts toward the worldwide, simultaneous development were based on the thought that market success would not just happen, but had to be planned. (Sir) Paul Giolami, the Group chief executive at the time, stated later:

> [Zantac] did not just come out. It was made here in every respect --- a whole team work, research, development. (Glaxo 1994, p.8)

Giolami also stated elsewhere, stressing the marketing function:

> Marketing has made that product as much as our research laboratories. For

> instance, in the United States where we had hardly started and in Germany and Japan where we were very small, we had to achieve two contradictory things: Make the most of Zantac and yet not hold back the development of our own company. That's when we came up with the idea of a co-marketing arrangement. We had the imagination and flexibility to hire a marketing team from a major company. (Glaxo 1987, p.10)

The co-marketing arrangement was to promote the product jointly with marketing partners in other countries. Its rationale was explained to be that any dilution of income would be offset by faster market penetration. The partners were Menarini in Italy, Cancan in Germany, Fournier in France, Hoffmann-La-Roche in the US and Sankyo in Japan. Glaxo also had its own marketing subsidiaries in these countries though their strength in each market was varied. (Glaxo 1987, p.17) These subsidiaries and the local partners in the same countries jointly promoted the drug. Even in the subsidiaries, local autonomy seemed to be regarded as important. John Wood put it:

> I think the most important thing, this is a really important thing, is that our entire company was built on a human network of devolution, or decentralization. ... In this case, they were not told what to do. They were given the product, and they were allowed quite a lot of freedom to do differently in different countries. ... The bosses of countries hired their people. ... Giolami's view was that the local people know best. (Interview)

The key role of marketing was shown by another activity, namely, persuading medical professionals. David Richards, the then medical director at Glaxo Group Research, was reported to say:

> By conducting clinical trials in all the main potential markets, we were able to create demand for the product among the opinion leaders before we actually launched. (Glaxo 1987, p.11)

Comparisons with cimetidine were fully utilised in the persuasion. It is easy to imagine that this tactic worked very well to take the existing market from cimetidine. John Wood put it:

> We've done a whole series of trials to compare ourselves with Tagamet. And we wrote many papers, to describe findings. And we were very

> fortunate because SmithKline had chosen a wrong dose. It's the dose which was not giving them the maximum effect. So we could use the dose of Zantac which gave a higher effect, both in ulcer healing and in maintenance. We had many chances to show that were repeated in other countries, and we showed that the lack of sexual side-effects, we showed that at high doses the side-effects got even worse with Tagamet. (Interview)

Wood also explained how they could take advantage of ranitidine's superior efficacy and duration to provide more convenient dosage compared with cimetidine:

> Tagamet was being given four times a day. ... Two pills at the bedtime to help you with acid over night. Five pills throughout a day. When we introduced Zantac, it was two pills, one in the morning, one at night. And then we did a whole series of big trials. And we made it converted to one pill a day, twice as big, at night, which worked just as well. ... And Tagamet tried to do that. They moved to 400mg twice a day which was not as good as their original dose, but more convenient. Then they moved to 800mg once a day, which was like a horse pill, and in that stage they were failing and losing. They had a big market share but we were taking more and more market share, as people learned the benefits of the product. (Interview)

Also Glaxo's internal documents stated:

> Zantac was marketed with the promotional messages, "Fast, Simple, Safe" which doctors interpreted as Faster, Simpler and Safer than Tagamet, although no such direct comparison was permitted in promotion[14]

There were also many papers by medical doctors in which ranitidine and cimetidine were compared and the superiority of ranitidine was reported. (Dowschke, Lux and Dowschke 1979; Zeldis, Friedman, Isselbagher 1983; Strum 1983)

The application of the drug was expanded. In 1984, ranitidine was reported to have superior results in maintenance treatment, that is, a smaller chance of relapse when it is taken continuously. (Gough et al. 1984; Silvis 1985; Glaxo 1987, p.11) This can be accepted if the side effects of a drug are low enough. This maintenance treatment was used as the most important concept for competition with cimetidine. It is

[14] In response to it, SmithKline and French promoted Tagamet as being "Tried and Trusted", according to the same document. On the promotion battle between Zantac and Tagamet, see also Angelmar and Pinson (1991), pp.7-8, pp.10-12, and Exhibit 19-23.

reported that Glaxo set out to persuade doctors that ulcers needed long-term, probably lifelong, maintenance treatment. (Angelmar and Pinson 1991, p.11 and Exhibit 22)

Many kinds of administration forms have also been developed. Wood put it:

> We did a lot of different pharmaceutical forms, so, normal tablets, larger tablets, effervescent tablets, injections, soft gel capsules, and syrup, and those, ... finally, we got permission in the US to move it over the counter so that you didn't need to get doctor's prescription, you are just going to a shop in the US, a pharmacy shop or supermarket or garage and buy some Zantac. That's the lowest strength. And by that stage we had treated two hundred and forty million people. (Interview)

These developments after the first product launch were quite intensely promoted by the company. Wood, again:

> I think it's fair to say that the company started off investing more and more and more as we went along. And I've worked on this drug for 16 years, and I never had any restriction on the amount of money I could spend. Now, in other words, I wanted to do this trial, that trial, that trial, [and they said] just "do it." So I was never, ever [constrained]. (Interview)

As a result of these marketing efforts, ranitidine overtook Tagamet sales on an annual basis and became the highest selling drug in the world in 1986. In 1988, its sales worldwide exceeded 1 billion pounds and its sales in the US exceeded 1 billion dollars. (Glaxo internal documents)

5.4. Famotidine

5.4.1. Introduction

Famotidine was the third marketed histamine H_2 antagonist, which was developed by Yamanouchi, a Japanese pharmaceutical company. Famotidine is said to be much more active than cimetidine. The imidazole ring of cimetidine is replaced with a 2-guanidinothiazole ring and the side chain is also changed to contain a

sulfonylamidine group. (Patrick 1995, p.309) This work was be done by Isao Yanagisawa and his colleague at Yamanouchi's Central Research Laboratories. Famotidine was launched on the market in Japan in 1985 (Yanagisawa 1994, p.167), in the US in collaboration with Merck in 1986 (Angelmar and Pinson 1991, p.12), and in about 80 countries by 1994. It has been the best selling histamine H_2 antagonist in Japan since 1988. (*Gekkan Mikusu*, Volume 24, No.14, December 1996, p.48) It was reported that famotidine in Japan enjoyed twice the sales of either ranitidine or cimetidine, but in the world its share was only about a third of that of ranitidine in 1993 and 1994. (*Scrip Yearbook*, 1995 Volume 1, p.129)

5.4.2. Making the Top Histamine H_2 Antagonist in Japan

A group of researchers of Yamanouchi began the search for anti-peptic-ulcer drugs in the mid-1970s. (Yanagisawa 1994, p.162) They had studied the application of prostaglandins until then. One possible application area for them was anti-gastric-ulcer. Their interest moved into the area, and began to look at other substances as well. Therefore, at the beginning, their search did not focus on histamine H_2 antagonists. Rather, their field of searching included broad types of anti-acid substances, including prostaglandins, histamine H_2 antagonists, and other substances. (Yanagisawa interview)[15] The chemical synthesis and biological screening began in August 1976, after the investigation of patents and literature. (Yanagisawa personal communication, September 1999) The research team consisted of four chemists, two pharmacologists, two assistants, and two researchers dedicated to the investigation of literature and patents, according to Yanagisawa. (Interview) Three lead compounds were chosen: one was discovered by Yamanouchi's researchers; the other was the compound originated from Schering; and the third was cimetidine, which was marketed and highlighted in the same year. (Interview) Because two of them were not H_2 antagonists, the pharmacological evaluation was done by both anti-acid activity and anti-histamine activity. (Yanagisawa 1994, p.162) The superiority of cimetidine was found in the course of the research in terms of potency and safety and it became the final lead compound. (Interview) They succeeded in replacing the

[15] The interview with Dr Isao Yanagisawa was conducted on 22nd January 1999.

cyanoguanidine part of the cimetidine molecule with cyano amidine and carbamoyl amidine parts.[16] (Yanagisawa, Hirata and Ishii 1984) Subsequently, they found that the compound containing the carbamoyl amidine had a histamine H_2 antagonist activity which is as strong as cimetidine. They also intended replacement of the imidazole ring of cimetidine, tried many kinds of rings, and discovered that the compounds with a 2-guanidinothiazole ring showed very strong H_2 antagonist activities. Eventually, they discovered that the compound that was the product of a combination of these two modifications was most active among all of the tested compounds. (Yanagisawa, Hirata and Ishii 1984; Yanagisawa 1989; Yanagisawa 1994) However, this compound was not stable enough to be industrialised. This instability was thought to be due to the carbamoyl amidine part and its replacement was considered. Because they had already tried many kinds of amidine derivatives, and the carbamoyl amidine derivative had been the best of all, the idea for further improvement almost ran out. A suggestion of the then director of the research laboratories to try sulfamoyl, which is slightly different from calbamoyl, opened the way to a solution. Yanagisawa was suspicious of the idea because sulfamoyl amidine derivative was supposed to be unstable as well and difficult to synthesise. Furthermore, the compound was not known in the previous literature. However, his team succeeded in the synthesis of the compound, and found that it was stable despite Yanagisawa's anticipation. (Yanagisawa 1994, pp.165-166) This compound is famotidine (Yanagisawa, Hirata and Ishii 1987; Yanagisawa 1989, pp.208-210; Belgian Patent 882071, 1980), which was reported to be about 30 to 40 times more potent than cimetidine *in vivo*. (Takagi, Takeda and Maeno 1982; Friedman 1987) 424 compounds had been synthesised and screened before they reached famotidine. (Interview) After the toxicological and pharmacological characteristics were confirmed to be satisfactory in the pre-clinical studies, the clinical trials of famotidine was started in 1980. The efficacy and safety of the drug were confirmed and it obtained an approval for manufacturing in January 1985. There seemed to be no significant problems after the synthesis to the launch, including scaling-up and organisational obstacles, despite difficult production conditions and modest

[16] Amidines were chosen because of their similarity to guanidines in terms of the chemical structure. (Yanagisawa 1989, pp. 203-206)

estimation of market size, according to Yanagisawa. (Interview) International development was made by Merck (US), and it was marketed in the US in 1986 and in other about 80 countries by 1994. (Yanagisawa 1994)

Famotidine rapidly took the market from cimetidine and ranitidine in Japan. In 1986, its sales exceeded that of ranitidine, and in 1988 it superseded cimetidine as the highest selling histamine H_2 antagonist in Japan. (*Gekkan Mikusu*, Volume 24, No.14, December 1996, p.48) In 1993-4, its share in the Japanese market was about twice greater than either that of ranitidine or that of cimetidine.[17] The success of famotidine in the Japanese market has been explained from several points. Firstly, it was reported to be much more potent than cimetidine. This meant fewer doses, which are convenient for the patients and doctors who want to control their patients' dosing. Secondly, it has been seen as having fewer side effects than cimetidine. It is said that these two points have been thoroughly emphasised by Yamanouchi's representatives. These are similar to the marketing tactics Glaxo adopted against cimetidine. Thirdly, the price of famotidine was set higher than that of cimetidine. (*Gekkan Mikusu*, Volume 24, No.14, December 1996, p.48)[18] This is beneficial for the company, given the quantity sold. Furthermore, unlike ordinary commodities, prescribed drugs can be sold in higher quantities despite being more expensive than rival products. In Japan, though the official prices, which are used at the reimbursement from the various health insurance programmes, are set under the fee schedule scheme, the real prices applied to the trading between hospitals and pharmaceutical companies are often lower than the official ones. The margin between the two prices (*yakka saeki*) constitutes a significant part of hospitals' and clinics' revenues. (Campbell and Ikegami 1998, p.148) Therefore, higher price can be welcomed by doctors and can result in the more frequent prescription. This has seemed to be the case in famotidine

[17] Market shares of famotidine, ranitidine and cimetidine in the Japanese anti-ulcer drugs in 1994 were reported to be 21%, 10% and 10% respectively. The total share of these three histamine H_2 antagonists was only 42% in Japan, whereas in the world their total comes to 58% in 1994. (*Scrip Yearbook*, 1995 Volume 1, p.129) This was because many kinds of traditional anti-ulcer drugs were still commonly used in the Japanese anti-ulcer drug market.

[18] Prices of pharmaceutical drugs in Japan are set by the Central Social Insurance Medical Care Council (*Chuikyou*), an advisory committee to the Minister of Health and Welfare under the national fee schedule (*shinryo hoshu*) scheme. This scheme is universal and virtually compulsory in Japan. (Campbell and Ikegami 1999, pp.16-19, pp.145-150)

compared with cimetidine, that is to say, the higher official price of famotidine has seemed to stimulate doctors' preference for the drug. (*Gekkan Mikusu*, Volume 24, No.14, December 1996, p.48) These three factors can explain the advantage of famotidine over cimetidine, but not over ranitidine. One possible reason why famotidine has surpassed ranitidine in the Japanese market share is the difference of sales forces. Yamanouchi regarded famotidine as the most important product to promote, while Nippon Glaxo, the main Japanese subsidiary of Glaxo, did not have such a large sales force, and Sankyo, the co-marketing partner of Glaxo in terms of ranitidine, had several other important drugs at the time to promote, which included their own products, and could not concentrate sales efforts only on ranitidine. (*Gekkan Mikusu*, Volume 24, No.14, December 1996, p.49)

The last point is interesting because it can also explain why famotidine could not be very successful in overseas markets.[19] The overseas marketing of famotidine was conducted by Merck (US), but the world's largest pharmaceutical company also seemed to be unable to concentrate its promotional resources on famotidine because of internal competition with other, more profitable, drugs introduced around the same time. (Angelmar and Pinson 1991, p.12)

A few other factors have been reported to contribute to the success of famotidine in the Japanese market. One of them is that it was emphasised in promotion that famotidine reinforced a protection factor in the stomach mucous membrane. (*Gekkan Mikusu*, Volume 24, No.14, December 1996, p.49) This activity was identified by using a new instrument, namely, an ultrathin endoscope. (Daneshmend et al. 1989) Another is that it has had an injection formula as well from the beginning of its market launch, which has been welcomed by hospitals. Furthermore, because of frequent additions in application, dosage and form, the company has had many opportunities to meet doctors and explain the drug to them. (*Gekkan Mikusu*, Volume 24, No.14, December 1996, p.49) Thus, famotidine has been the top selling

[19] Worldwide market shares of famotidine, ranitidine and cimetidine in anti-ulcer drugs in 1994 were reported to be 12%, 35% and 11% respectively. Market share of each in the US was 11%, 48%, 14% respectively and in the Europe 7%, 40%, 8% respectively in the same year. (*Scrip Yearbook*, 1995 Volume1, p.129)

histamine H_2 antagonist in Japan, but has had smaller sales than ranitidine in the world.

5.5. Discussion

5.5.1. Paradigmatic Innovation and Modification-based Innovation

The discovery of cimetidine (including burimamide and metiamide as its prototypes) is a paradigmatic discovery, whereas that of ranitidine or famotidine is a normal-scientific discovery. (See Section 3.5.2.) The discovery of cimetidine changed the theory of gastric acid secretion radically. A general belief that the key relevant substance in gastric acid secretion was gastrin was replaced by another that it is histamine. People now believe that there are two different subtypes of histamine receptors after the discovery of cimetidine. The discovery also changed the treatment for peptic ulcer. After the advent of cimetidine, peptic ulcer seems to be the jurisdiction of physicians, not that of surgeons as before. In contrast, the discovery of ranitidine and of famotidine did not change the theory and therapy established by the discovery of cimetidine, but supported and promoted them.

This difference reflected the level and characteristics of uncertainty surrounding the process of discovery and development of these drugs. In the case of cimetidine, scientific, technological and business uncertainties were extremely high. Scientifically, histamine had been discounted as a key to the physiology of gastric acid secretion. Technologically, there was no exemplary compound that inhibited the acid secretion by antagonising histamine receptors. Even the way of assay to find such activity was not known. From the business point of view, it was considered doubtful that medical practitioners would accept such drugs even if the companies fortunately succeeded in their discovery.

This high uncertainty accompanying paradigmatic discovery created distinguishable profiles in the other aspects of innovation, especially in the organisation and in the market. In the organisation, the research team at SmithKline & French faced much

severer organisational resistance than its counterparts at Glaxo and Yamanouchi. Even within the research team, it is reported that there was significant suspicion about the possibility of such a drug. The parent company was about to axe the project when there had been no outputs for years. In those circumstances, it was the charismatic leadership of James Black that kept the project alive. Because of his outstanding achievements in the work on β-blockers at ICI, and his strong enthusiasm about new histamine receptors, the research team was prevented from deviation from histamine antagonists and the company did not dare to scrap the project. It was probably fortunate for them that the research site was geographically distant from the head office of the company so that they could have autonomy to some extent. The British subsidiary had to think about its own survival in the company group and its members might have shared the senses of crisis and unity. Therefore, the British company succeeded in concentrating its resources on the histamine H_2 antagonist project after 1968 when they found SK&F 91486, a weak antagonist of histamine H_2 receptors. In order to persuade people inside and outside the company, they invented the concept of histamine H_2 receptors and hurried to make the results public when they discovered burimamide, though it was hopeless as a pharmaceutical drug.

In contrast, in the cases of ranitidine and famotidine, at least, scientific and technological uncertainties were lower than in cimetidine. The existence of histamine H_2 receptors had already been known. The researchers at Glaxo and Yamanouchi had exemplary compounds including burimamide, metiamide and cimetidine, though some of their properties were as yet unknown. They had also exemplary methods of assay. They knew a significant part of the problems their precursors had faced. Their companies were probably more supportive than SmithKline and French in the US, though the eventual size of the market seemed to be unclear at that time.

However, the research teams in Glaxo and Yamanouchi faced different problems from those their counterpart in SmithKline and French did. They had to make something different and better in practice. The Glaxo team started from burimamide and the Yamanouchi team started from cimetidine, but both groups had to

circumvent the patents of SmithKline and French if they wanted to enjoy their income fully. Each of them also had to make a drug which is at least as good as cimetidine, but with some additional advantages over cimetidine to promote its drug effectively. Yamanouchi also had to circumvent Glaxo's patents and find further additional advantage over ranitidine. Therefore, what they had to do was only modification, but modification was not at all easy because there were not only natural restrictions but also social restrictions.

In addition, because it was obvious that the delay of the launch meant loss of the income, Glaxo and Yamanouchi had to develop their own histamine H_2 antagonists very efficiently. This was achieved by doing different tasks in parallel[20] (Glaxo 1987, p.11; Glaxo internal documents; Interview with plant managers at Yamanouchi[21]), which was apparently similar to the concurrent engineering in the machine industry but different from it in that neither production specialists nor marketing specialists took part in the drug design process.[22]

In the promotion, differences between the previous product(s) and theirs had to be emphasised. Secondary advantages such as smaller dosage, longer duration, lack of minor side effects, variety of forms and additional activities were emphasised. In the ranitidine case, an important additional activity was the maintenance treatment, while in the case of famotidine, it was the protection of the mucous membrane. They used academic papers as evidence for their claims. In the famotidine case, new experimental instruments helped to identify an additional activity. These efforts of persuasion were directed outside of the company, mainly, to doctors.

Because both Glaxo and Yamanouchi were mainly domestic companies at the time, they had to ally themselves with overseas companies. This turned out to have both advantages and disadvantages. If the choice of partner was right, the co-marketing could exploit the market very rapidly. Glaxo was very successful in most countries

[20] SmithKline and French also adopted the parallel approach in the development of metiamide and cimetidine, as we saw in Section 5.2.2.
[21] The interview with plant managers at Yamanouchi was conducted on 17th September 1996.
[22] On the concurrent engineering, see Clark and Fujimoto (1991), pp.211-217.

because of this. However, if they chose a "busy" partner, this did not work. Yamanouchi chose Merck as an overseas partner and could not enjoy a large share outside Japan. Glaxo chose Sankyo as a Japanese partner and could not obtain a large part of the Japanese market. The national health care system seemed to support the exceptional success of famotidine in Japan. Because of its higher price, that is, because of higher opportunity to gain margin under the system, doctors probably preferred to prescribe it.

In sum, the innovation process of cimetidine was characterised by high scientific and technological uncertainty, stronger organisational resistance, the powerful leadership of the project leader, a new concept that changed theory and therapy, and an exemplary role of the compound. In contrast, the innovation process of ranitidine and famotidine was characterised by lower scientific and technological uncertainty, the social restriction on modification, the organisational pressure of efficiency, the systematic and intensive efforts in development, and the creation of differences from existing rivals. From these we can identify two types of innovation in the pharmaceutical industry. The first type is represented by the case of cimetidine and I name it paradigmatic innovation, not only because it is based on paradigmatic discovery but also because every aspect of the innovation process is paradigmatic. The second type is represented by the cases of ranitidine and famotidine. This is named modification-based innovation rather than normal-scientific innovation, because socially acceptable and distinguishable modification is regarded as the most important element in this type of innovation, whereas its normal-scientific aspect in discovery is less important in the whole process of innovation.

These two types of innovation do not necessarily link to the business performance. Ranitidine was more successful in business than cimetidine, though the former is a modification-based innovation and the latter is a paradigmatic innovation. Famotidine was not so successful as ranitidine in the world, though it was also a modification-based innovation. However, it was most successful of the three histamine H_2 antagonists in Japan.

5.5.2. Rational Drug Discovery?

Although cimetidine was popularly regarded as discovered by a rational approach, it does not seem the case when we look at the process closely. It seems true that a rational and theoretical approach was adopted in various parts of the process, but trial and error also played a significant role. This seems the same as in the cases of ranitidine and famotidine.[23] In other words, in these discoveries, new knowledge obviously came from not only existing knowledge that the researchers possessed, but also from interactions of compounds and organisms. We cannot attribute the processes only to social process or cognitive process. We must take nature into account as well.[24] This also has another important implication for the innovation study. In the linear model of innovation, it is assumed that development follows research. However, as revealed in the case of metiamide and cimetidine, in the pharmaceutical industry, as well as other industries, some problems arise in the stage of development, and they sometimes force the project to go back to the research stage again. This reversal from development to research is probably not very apparent because the drugs that failed in the development process are thrown away before the market launch, and their relationship with their successors is unlikely to be clear for outsiders. Unexpected interaction between compounds and organisms often causes problems which may induce the reversal from development to research.

[23] In burimamide case, about 700 compounds, in ranitidine, hundreds of compounds (Palmer interview), and in famotidine, more than 400 compounds were synthesised.
[24] The discovery of *Helicobacter pylori* in the stomach is another example which reminds us of a essential part that nature plays in the knowledge creation. See Thagard (1999), pp.39-83.

Chapter 6: LHRH Analogues

6.1. Introduction

The drugs that we examine in this chapter are called luteinising hormone releasing hormone (LHRH) analogues, which are used for the treatment of prostate and breast cancer, endometriosis and some other sex-hormone-dependent diseases. LHRH is a hormone secreted from the hypothalamus in the brain, and it stimulates the secretion of luteinising hormone (LH) from the pituitary gland. LH, in turn, stimulates the secretion of testosterone from the testes in males, or stimulates oestrogen production, ovulation and the development of the corpus luteum in females. Therefore, LHRH is a hormone that fundamentally regulates growth and activities of the gonads, so its analogues can be used for the treatment of various diseases in sex organs or the control of reproduction in human and other animals. The two LHRH analogues that we examine in detail here are leuprorelin acetate (hereinafter, leuprorelin) developed by an alliance between Takeda in Japan and Abbott in the US, and goserelin developed by ICI Pharmaceuticals (now AstraZeneca) in the UK. They are the most successful LHRH analogues on the market in the world. Leuprorelin was synthesised in 1973 by a group of scientists at Takeda led by Masahiko Fujino. Goserelin was discovered in 1976 by Anand Dutta and Barry Furr at ICI Pharmaceuticals. However, what made these drugs highly successful in the market was the development of their depot preparations, which can release the drugs very slowly within the body. Frank Hutchinson and Barry Furr at ICI Pharmaceuticals achieved the development of the depot preparation[1] for goserelin in 1981. Yasuaki Ogawa and his colleagues at Takeda developed the equivalent for leuprorelin in 1984. Leuprorelin was first marketed with a preparation for daily injection in the United States in 1985. Then its depot preparation was launched in the US in 1989 and in Japan in 1992. Goserelin was marketed as its depot preparation from the start. It was launched first in the UK in 1987, then in the US in 1990 and in Japan in 1991.

[1] The word "formulation" in place of "preparation" is often used among the experts in the area.

Fig 6.1 Compounds Discussed in This Chapter

*Underlines show replacement.

a) LHRH

amino acids: pGly – His –Trp – Ser –Tyr – Gly – Leu – Arg – Pro – Gly – NH_2

position: 1 2 3 4 5 6 7 8 9 10

b) TAP-031

pGly – His –Trp – Ser –Tyr – Gly – Leu – Arg – Pro – $\underline{NHCH_2CH_3}$

c) Leuprorelin

pGly – His –Trp – Ser –Tyr – $\underline{\text{D-Leu}}$ – Leu – Arg – Pro – $\underline{NHCH_2CH_3}$

d) Triprorelin

pGly – His –Trp – Ser –Tyr – $\underline{\text{D-Trp}}$ – Leu – Arg – Pro – Gly – NH_2

e) Goserelin

pGly – His –Trp – Ser –Tyr – $\underline{\text{D-Ser(Bu}^t\text{)}}$ – Leu – Arg – Pro – $\underline{\text{azaGly}}$ – NH_2

f) Buserelin

pGly – His –Trp – Ser –Tyr – $\underline{\text{D-Ser(Bu}^t\text{)}}$ – Leu – Arg – Pro – $\underline{NHCH_2CH_3}$

Table 6.1: Major Events Related to the Discovery and Development of LHRH Analogues

Year	Leuprorelin	Goserelin
1960	Discovery of LRF (LHRH)	
mid1960s	Basic research start (Abbott)	Basic research start (ICI)
1971	Research start (Takeda)	
	Discovery of LHRH structure	
1972	TAP-31 discovered	
1973	Discovery of leuprorelin	
1975-6	Discovery of paradoxical effects	
1976		Discovery of goserelin
1979		Depot preparation research start
1981	Depot preparation research start	Depot preparation developed
1984	Depot preparation developed	
1985	Launch in the US (daily injection)	
1987		Launch in the UK
1989	Launch in the US (depot preparation)	
1990		Launch in the US
1991		Launch in Japan
1992	Launch in Japan	

6.2. Discovery of LHRH

The idea that the brain has an influence on the reproductive system via the pituitary gland was suggested in the 1930s. Since then, a number of scientists had done anatomical and physiological studies on the cerebral regulation of hormone secretion from the pituitary gland. (Harris, Reed and Fawcett 1966; Harris 1972; Schally et al. 1968; Burgus and Guillemin 1970) Geoffrey Harris in England was one of the leading researchers in this area. In 1947, he and J. D. Green proposed that this regulatory system worked by means of a humoral relay through the tiny vessels that linked the hypothalamus in the brain with the pituitary gland. (Green and Harris 1947) This idea was not immediately accepted. (Wade 1978, 210) For example, Thomson and Zuckerman (1953) claimed that the vessels that Harris had reported did not form the pathway of chemical transmitters. Harris argued back that Zuckerman's experiment had flaws. (Harris 1955, pp. 87-88) However, to convince others of his idea, Harris had to find the substance, which was secreted from the hypothalamus and stimulated the release of hormones such as luteinising hormone (LH). Not only Harris but also some other researchers in the world, including Samuel McCann, Roger Guillemin and Andrew Schally in the United States, addressed this problem. (Harris, Reed and Fawcett 1966; Harris 1972; Schally et al. 1968; Burgus and Guillemin 1970; Wade 1978, 210-211)

In 1960, McCann's research team in Pennsylvania reported that extracts of a part of the hypothalamus stimulated the secretion of LH from the pituitary gland in rats. They suggested the existence of an LH-releasing factor in the hypothalamus. (McCann, Taleisnik and Friedman 1960; McCann 1962) At about the same time, Harris's team independently found that extracts of a part of the hypothalamus caused ovulation when infused into the pituitary gland in rabbits. They concluded that the hypothalamus contained a specific substance which stimulated the release of the gonadotrophic hormone such as LH. (Campbell, Feuer, Garcia and Harris 1961; Harris, Reed and Fawcett 1966, 268) Guillemin's team confirmed these results in 1961 by using extracts of rat and sheep hypothalamus. (Guillemin 1964; Harris, Reed

and Fawcett 1966, 268) The LH-releasing factor was speculated to be polypeptide from its properties as early as 1962. (McCann 1962; Guillemin 1964)

There was keen competition between McCann, Harris, Guillemin, Schally and Karl Folkers for isolation and molecular characterisation of the LH-releasing factor. (Wade 1978, 302-303; Wade 1981, pp. 183-226) In particular, Guillemin and Schally concentrated their efforts on obtaining the molecular structure of the LH-releasing factor, whereas Harris and McCann also paid attention to physiological aspects of the substance. (Wade 1978, 358; Harris and Naftolin 1970; Latour and Woolgar 1986, pp.117-119) Guillemin and Schally had already engaged in severe competition for the structure of another hypothalamic hormone called thyrotropin-releasing factor (TRF; or thyrotropin-releasing hormone, TRH) from around 1962 to 1969, before they began to pour their full energy into the investigation on the structure of the LH-releasing factor.[2] (Latour and Woolgar 1986, pp.105-150; Wade 1978; Guillemin 1978; Schally 1978) In the previous competition over TRF (H), Guillemin and Schally redefined the name of the game in discovery of hypothalamic hormones. Discovery of a hormone was redefined as the identification of its molecular structure by using methods acceptable to peer scientists. To find a substance having an activity or to speculate its molecular structure without recognised methods became insufficient to constitute discovery of a hormone. This new rule was essential to the practical use of these hormones in therapy, because natural supply of these hormones was very limited (only 250 micrograms of LH releasing factor from 160,000 pig hypothalami[3]) and so they had to be synthesized. What was also important was that this new definition of discovery changed the financial requirement for participating in the competition for discovery. It became necessary for each research team to buy expensive, sophisticated analytical equipment and obtain millions of animal hypothalami in order to compete effectively. (Latour and Woolgar 1986, pp. 118-124, pp.134-143) It should be noted that it was unclear at that time whether the substance really existed or not, whether it was a polypeptide or not, and whether it was an

[2] Guillemin and Schally "independently" determined the structure of TRF(H) in 1969. Both of them won the Nobel Prize in Physiology or Medicine in 1977 in recognition of their contribution to research on hypothalamic hormones.
[3] Wade (1981), p. 205

unknown substance or not. (Latour and Woolgar 1986, pp. 116-117) Therefore, it was very risky to invest huge amounts of money into this competition for the molecular structure. Probably, the uncertainty about the search of the structure of LHRH was considerably reduced after the identification of the structure of TRF (H), but this did not happen until 1969. Fortunately for Guillemin and Schally, both of them managed to obtain huge financial support from organisations such as the National Institute of Health or the Veteran Administration, although this support considerably increased the pressure on them to hasten the research. (Wade 1978, 221; Wade 1981, p.197; Latour and Woolgar 1986, p.139) Because of these factors, Gullemin's and Schally's groups managed to take the lead in the competition for the structure of LHRH over the other groups, even though they began to concentrate on LHRH as late as 1969. Of course, they and their collaborators were creative and skilful researchers. However, Guillemin and Schally might not have caught up with the other groups without the combination of the more demanding definition of hormone identification and characterisation they had established, their research priority, their risk-taking attitude to the high uncertainty in the area and their financial resources. (Wade 1981, p. 199. pp. 220-224)

In 1971, Schally's team finally reported the molecular structure of the LH-releasing factor in pigs. Two Japanese chemists, Hisayuki Matsuo and Yoshihiko Baba, and a Japanese physiologist, Akira Arimura, crucially contributed to the discovery. (Wade 1981, pp. 204-214) It was a decapeptide, that is, it consisted of ten amino acids. (Fig. 6.1a) (Matsuo et al. 1971) LHRH, which had been Schally's terminology (Schally et al. 1968), became widely accepted as the name of the substance. Soon after that, Guillemin's team confirmed an identical structure of LHRH in sheep. (Burgus et al. 1972; Amoss et al. 1971) It is reported that shortage of the LH-releasing factor delayed Roger Burgus, Guillemin's chemist collaborator, in his efforts to determine the structure of the substance. (Wade 1978, 302) Harris's team was also said to be close to discovering the structure at that time. (Harris 1972, xiv; Gregory 1971, p.21; Furr interview[4]) It was not only analytical chemistry but also synthetic chemistry that contributed to the discovery of the structure of LHRH. Synthesizing the replica of a

[4] The interview with Dr Barry Furr, one of the discoverers of goserelin at ICI Pharmaceuticals Division (now AstraZeneca), was conducted on 21st July 1999.

speculated substance and then examining its biological activities was a major tool to reveal or confirm the molecular structure of the substance. (Latour and Woolgar 1986, p. 144; Wade 1981, p.212) Schally's group succeeded in the synthesis of LHRH, too, in 1971. (Matsuo, Arimura, Nair and Schally 1971; Schally et al. 1971b) The research team of Karl Folkers, who was a former collaborator of Schally's in his TRH project, also succeeded in synthesizing LHRH and confirming its biological activity, soon after Schally's announcement of the LHRH structure. (Sievertsson et al. 1971)

Because LHRH was supposed to regulate the reproductive system, several pharmaceutical companies recognized its medical and commercial potential early on. Two companies were involved in the discovery of LHRH. In England, ICI's Pharmaceuticals Division was in collaboration with Harris. (Harris 1972, xii-xiv; Gregory 1971) In the United States, Wilfrid White at Abbott Laboratories collaborated with Schally in research on both follicle stimulating hormone-releasing hormone (FSH-RH) and LHRH.[5] (Schally et al. 1968, 537-538, 548-550; Schally et al. 1971a) In addition, researchers at Hoechst in Germany independently succeeded in synthesizing LHRH only three months after the first announcement of its structure. (Geiger et al. 1971)

6.3. Synthetic LHRH Analogues: an Overview

Even before the structure of LHRH was announced, analogues of LHRH as well as LHRH itself began to be synthesized and examined by various research groups, including the groups involved in the competition for the structure of LHRH, in order to confirm the structure. (Monahan et al. 1972; Chang et al. 1972; Schally et al. 1972; Geiger et al. 1972; Fujino et al. 1972a; Yanaihara et al. 1972) The early purpose of the synthesis of LHRH analogues was to understand the structure-activity relationship for the hormone and to create a synthetic antagonist of LH-release (Schally et al. 1972, 366; Vale et al. 1972, 933; Monahan, Amoss, Anderson and Vale 1973, 4616, 4619), rather than to find a more potent agonist. This was because

[5] The two hypothalamic hormones were found to be identical later. (Schally et al. 1971a; Matsuo et al. 1971; Schally, Arimura and Kastin 1973, 344; Besser and Mortimer 1974, 176)

antagonists of LH-release were thought to be useful for contraception, whereas LHRH itself could be used as a pro-fertility drug. (Besser and Mortimer 1974, 178) However, when several analogues were found to be more potent than LHRH in these efforts, their clinical potential as pro-fertility agents began to gather more attention.

In 1972, Masahiko Fujino at the Central Research Division of Takeda Chemical Industries found that an analogue with modification at position 10 of LHRH molecule (Fig. 6.1b) was five times more potent than LHRH. (Fujino et al. 1972b) In the next year, Michael Monahan and his colleagues at the Salk Institute, where Guillemin was leading the research, reported that several analogues with modification with D-amino acids (optical isomers) at position 6 had several times higher potency than LHRH. (Monahan, Amoss, Anderson and Vale 1973) In 1974, Fujino and his colleagues found that several analogues with modification at both position 6 and position 10 of the molecule was up to about a hundred times as potent as the original substance. One of these was leuprorelin (Fig. 6.1c), the story of which we examine in detail in the following section. (Fujino et al. 1974a; Fujino et al. 1974b; Rippel et al. 1975) Schally's group reported similar results around the same time. (Coy et al. 1974; Vilchez-Martinez et al. 1974) Coy and Schally (1978) estimated that about 700 analogues of LHRH had been synthesized by 1978. Among them were included four analogues marketed later: leuprorelin synthesized and developed by an alliance of Takeda and Abbott, triptorelin by Schally's group (Coy et al. 1975), goserelin by ICI (Dutta, Furr, Giles and Valcaccia 1978) and buserelin by Hoechst (Sandow, von Rechenberg, Jerzabek and Stoll 1978). (Fig. 6.1d-f) All but triptorelin are analogues modified at both position 6 and position 10 of the LHRH molecule.

These highly active analogues of LHRH, so-called "super-active" agonists were at first thought to be useful for stimulating fertility. However, when these compounds (including synthetic LHRH) were tested in laboratories and hospitals in the mid-1970s, it was found that they had a paradoxical effect: their repeated administration did not stimulate but eventually inhibited reproductive function in animals and humans. (Oshima et al. 1975; Corbin and Beattie 1975; Banik and Givner 1975;

Rippel and Johnson 1976; Happ et al. 1978) This was speculated to be due to the phenomenon of "desensitisation" or "down-regulation" of the physiological processes responsible for LHRH release. (Hsueh, Dufau and Catt 1977; Belchetz et al. 1978; Rivier, Rivier and Vale 1978, 2303; Sandow 1983, 571-575; Furr and Woodburn 1988, 535) This discovery of the paradoxical effect led researchers to alternative applications: including treatment for breast cancer (Johnson et al. 1976), contraception (Beattie and Corbin 1977), treatment for prostate cancer (Redding and Schally 1981; Warner, Santen, Demers and Max 1981), treatment for idiopathic precocious puberty (Crowley et al. 1981), treatment for endometriosis (Meldrum et al. 1982), treatment for uterine fibroids (Filicori et al. 1983) and some other applications (Corbin 1982; Sandow 1983; Waxman 1984; Cutler et al. 1985; Furr and Woodburn 1988). These applications became much more important than the short-term pro-fertility use, which had originally been regarded as the main application. It should be noted that the development of these various applications was simultaneously conducted by different research groups with different analogues. We examine the development of applications of two analogues, leuprorelin and goserelin, in detail in the following sections. However, other analogues also contributed to the development of their various clinical applications. These include buserelin (Jacobi and Wenderoth 1982; Faure et al. 1982; Waxman et al. 1983a, b [treatment for prostate cancer]; Klijn and de Jong 1982 [treatment for breast cancer]; Lemay and Quesnel 1982 [treatment for endometriosis]; Labrie et al. 1984 [combination therapy of prostate cancer with antiandrogens]; Maheux et al. 1984 [treatment for fibroids]), triptorelin (Redding and Schally 1981; Tolis et al. 1982 [treatment for prostate cancer]; Redding and Schally 1983 [treatment for breast cancer]) and D-Trp^{6}- Pro^{9}-NEt-LHRH synthesized and developed by the Salk Institute (Rivier, Rivier and Vale 1978 [contraception]; Crowley et al. 1981[treatment for idiopathic precocious puberty]; Meldrum et al. 1982 [treatment for endometriosis]; Filicori et al. 1983 [treatment for fibroids]; Comite et al. 1986 [treatment for central precocious puberty]).

Another important aspect in the development of LHRH analogues was the development of novel preparations (or formulations). Although "super-active"

LHRH analogues were longer acting than LHRH itself, it was necessary that they were given daily in order to obtain the long-term paradoxical effect. Oral administration did not produce a clinically effective activity. Therefore, daily injection was the first preparation, by which leuprorelin was approved by the Food and Drug Administration in the USA. Because of the lack of convenience of this preparation in particular in countries where self-injection was not generally allowed, various other preparations were developed. The second preparation was a nasal spray preparation developed by Hoechst for buserelin. As the third preparation, ICI developed a biodegradable, sustained-release preparation in the early 1980s, which is described in detail in Section 6.5. (Furr and Woodburn 1988, 536) The fourth preparation was the one using biodegradable injectable microcapsules, adopted by Syntex for their LHRH analogue called nafarelin (Sanders et al. 1984), Schally's group for triptorelin (Reddings, Schally, Tice and Meyers 1984) and Takeda for leuprorelin (Ogawa, Okada, Heya and Shimamoto 1989). These biodegradable preparations were different from each other in composition and/or in production methods. All of these new preparations greatly contributed to the diffusion of these medicines. It should be noted that they were also developed by various research groups. However, due to limitation of space, in the following sections, we look closely only at the processes of discovery, development of application and development of preparation, in two highly successful LHRH analogues, leuprorelin and goserelin.

6.4. Leuprorelin

Leuprorelin (leuprolide, in the US) is the first marketed LHRH analogue, discovered and developed by the alliance of Takeda Chemical Industries in Japan and Abbott Laboratories in the US. It was synthesized by a research team led by Masahiko Fujino at Takeda. Fujino, around 1965, studied synthesis of peptides under D. N. Ward, one of Guillemin's co-workers, at the University of Texas. Fujino witnessed the keen competition between Guillemin and Schally over TRH there and was interested in hypothalamic hormones such as TRH and LHRH. He described the situation:

> At that time, it was still very hard to synthesize peptides. If you had been able then to combine five amino acids, you would have been able to get a PhD. ... It was suggested to me [by a Japanese professor] that I do characterization and synthesis of TRF at Texas, but when I went there, it hadn't been isolated yet. So I couldn't do that. Instead, I worked on LH, luteinising hormone, there.
> ...
> [Guillemin, Schally and McCann] were really fighting each other. ... I saw them spending enormous amounts of money. I saw a ceiling of the laboratory removed to set up huge columns for chromatography for the isolation [of the hypothalamic hormones]. I saw a number of excellent researchers really seriously working on the substances, and thought that something unusual must be going on. I felt that something extraordinary would happen when the substances were identified. I was really impressed. (Fujino interview[6])

After Fujino came back to Japan, he was involved in the research on the synthesis of adrenocorticotrophic hormone (ACTH) and gastrin derivatives for a while. (Fujino interview; Takeda 1983, p. 753) When the isolation and characterisation of TRH was announced in 1969, he started research on the synthesis of TRH, because he had been interested in it since his stay in Texas. The objective was to find a simple and economical way of synthesizing TRH. His team succeeded in synthesizing TRH on a large scale in 1974, and it was marketed in 1978. (Fujino 1992, p. 2; Fujino interview; Takeda 1983, p.743, pp.1006-1007) This experience gave Fujino confidence in peptide research. He said:

> What I thought first was that [TRH] would become a drug if I could produce it at the level of kilograms. Because the substance was very active, we didn't need more. At that time, you could announce that you had made it if you could make only a few milligrams of it. ... So, when I succeeded in making TRH in kilograms, my confidence grew. I was convinced that I could make drugs from peptides. (Interview)

Meanwhile, Abbott proposed to Takeda that they collaborate in research on hypothalamic hormones in October 1970. Abbott had been in particular interested in LHRH and its analogues. As mentioned above, the company had helped Schally's group to identify the molecular structure of LHRH. The company chose Takeda as its partner because Abbott's research staff including Wilfred White knew that Fujino

[6] The interview with Dr Masahiko Fujino was conducted on 28th January 1999.

and his colleagues at Takeda did good work on the synthesis of peptides. Fujino also knew White's work in the area. Takeda accepted the proposal and they made a contract of research collaboration in August 1971. Shortly before that, the molecular structure of LHRH had been announced. The two companies at first agreed that Takeda would do the synthesis of LHRH analogues and Abbott would do biological tests of them. Although Takeda had an excellent ability in synthetic chemistry, it did not have the *in vitro* assay for the hormone. However, each company learned the other's skill and later began to do both synthesis and biological tests. They exchanged information and material, but otherwise, worked quite independently. (Takeda 1983, 743; Fujino 1992, p.3; Fujino interview; Kuwashima 1996. p. 119; Arnold et al. 1974)

Fujino's team started the synthesis of LHRH analogues around the end of 1971. The initial objective was to get a fertility stimulant. The methods they had developed for the synthesis of TRH were partly applied to this work and made it efficient. At first, replacement of every position of amino acid was tried. (Fujino et al. 1972a; Fujino 1992, p. 4) However, the results were disappointing. All the early analogues were much less potent than LHRH. Then they tried the replacement of glycineamide (Gly-NH_2) at position 10 with various alkylamines, which have a similar size to glycineamide. Fujino focused on position 10 because it was speculated that an enzyme destroyed the LHRH molecule at that position. Fortunately for him, the method his team was using for the synthesis, the liquid-phase method, was suitable for this replacement, whereas the more commonly used solid-phase method was not. (Fujino interview) Fujino had chosen the liquid-phase method because he had regarded it as better in producing a large quantity of peptide fragments, though there had been different opinions about the value of these methods at that time. (Fujino personal communication, August 2000) Among them, an analogue (TAP-031), which was replaced by ethylamide, showed high potency, 5 times as potent as LHRH in the ovulation-inducing assay. (Fujino 1992, pp. 4-5; Fujino et al. 1972b; Fujino et al. 1973a; Fujino et al. 1973b; Rippel et al. 1973) This was the most potent LHRH analogue at that time and indicated to others that the replacement at position 10 was effective in enhancing the potency of LHRH analogues. TAP-031 was marketed later

as a fertility stimulant for cattle, but failed to be a drug for humans because its administration for this purpose, the frequent injection, was not practicable. (Fujino 1992, p. 5; Fujino interview; Takeda 1983, pp.1035-1036)

Fujino and his colleagues then tried replacement of amino acids at other positions, while keeping the modification of position 10. Fujino noticed glycine at position 6. He explained the reason:

> I noticed it because only glycine has no side chain. So, I thought that this was probably essential for the molecule to be bent. ... When we replaced it with another amino acid, the activity disappeared. I thought this was due to the bend of the molecule. So, I tried D-amino acids rather than ordinary L-amino acids to change the bend at position 6. Then, the activity remarkably increased. I've got it, I thought. (Interview)

Two episodes showing the serendipitous aspect of this discovery were also reported. First, when a young researcher was told by Fujino to link an ethylamide to position 10, he did it wrongly to position 9, but the resultant peptide showed a high potency. This made Fujino notice the replacement of position 10. Second, another young researcher simply replaced an amino acid at position 6 with another, and the resultant LHRH analogue showed an astonishing activity. However, other skilled researchers failed to reproduce the experiment. Fujino did not ignore this happening. He made the researcher check every amino acid he had used. Then, it was found that the amino acid used at position 6 was not an L-amino acid but a racemic amino acid, which is a mixture of two optical isomers, an L-amino acid and its D counterpart. A racemic amino acid is the crude product of amino acid synthesis. The young researcher used the crude synthetic amino acid, which should have been divided into the two isomers. However, this event turned Fujino's attention to the bend at position 6. (Ogawa and Fujino 1994, pp. 176-177)

As mentioned in Section 6.3, Monahan at the Salk Institute independently found that the replacement of glycine at position 6 with a D-amino acid produced a several times more potent LHRH analogue. (Monahan, Amoss, Anderson and Vale 1973) However, when Fujino and his colleague combined the replacement at position 6

with the replacement at position 10, they obtained 50 to 80 times more potent analogues in ovulation-inducing activity in rats. (Fujino et al. 1974a; Fujino et al. 1974b; Fujino 1992, pp.5-6) The activity of these analogues was not so remarkable *in vitro*: at most several times. Fujino explained the difference between *in vivo* and *in vitro*:

> You cannot know how strong the activity is, *in vitro*. You can know only whether the activity is strong. *In vitro*, the activity did not appear so strong. But in animals, it showed an outstanding activity. This is because its action lasted [in animals]. ... *In vitro*, you measure only one release. So, you cannot know [its whole activity]. (Interview)

Among the several analogues substituted at position 6 and position 10, the most potent one, [D-Leu^6, des-Gly-NH_2^{10}, Pro-ethylamide^9]-LHRH (TAP-144, leuprorelin), was chosen for the clinical development, aiming at the induction of ovulation in infertile women. (Fujino et al. 1974b; Rippel et al. 1975; Fujino 1992, p.6)[7] In the end, they synthesized about 150 LHRH analogues to obtain this one. (Fujino 1992, p.4)

However, in the process of pre-clinical studies, researchers at Abbott noticed the paradoxical effect of "super-active" agonists, mentioned in Section 6.3. When they gave a large dose of leuprorelin continuously to rats to examine its long-term toxicity, they found that it inhibited ovarian and uterine growth and that it caused atrophy of some sex organs such as the uterus and the epididymis. (Rippel and Johnson 1976; Fujino interview) Several similar observations were reported outside the company at the time. (Oshima et al. 1975; Corbin and Beattie 1975; Banik and Givner 1975) Knowing that the drug acted as if it were an antagonist in the long term, they began to look for alternative applications such as the treatment of sex hormone-related cancer. It was still possible to develop the drug as an ovulation-inducing drug. However, from the point of view of clinical usefulness and profitability, anti-cancer application became the priority. (Kuwashima 1996, p.121) It had been known that the growth of breast cancer and that of prostate cancer were dependent on the level of

[7] [D-Ala^6, des-Gly-NH_2^{10}, Pro-ethylamide^9]-LHRH was about as potent as leuprorelin, but the latter was better from the viewpoint of production. (Fujino personal communication, August 2000)

sex hormones in the blood. (E.g. Jensen et al. 1971; McGuire, Chamness, Costlow and Shepherd 1974 [on breast cancer]; Huggins, Stevens and Hodges 1941; Byar 1973 [on prostate cancer]) Because the drug could ultimately reduce the level, the researchers thought to use it for the treatment of breast cancer first. They confirmed that the drug led to mammary tumour regression in rats. (Johnson, Seely, White and DeSombre 1976) However, Fujino pointed out uncertainty in this area:

> It was not clear. At that time, it was said that too much steroid [sex] hormone caused breast cancer, but it didn't show up when measured. Also, patients of prostate cancer weren't necessarily rich in the male hormone. Anyway we tried. When we tried [leuprorelin], it surely worked in animals. ... So, there must be a relationship [between sex hormones and cancer]. But this isn't very clear even now, though it has become somewhat clearer after the advent of the inhibitory "super-agonists." (Interview)

The clinical trials of leuprorelin for the treatment of breast cancer failed to show very good results. (Harvey et al. 1981) Fujino claimed that this was due to contextual reasons rather than the efficacy of the drug itself.[8]

> Because surgical treatment was known to be quite effective in breast cancer, the drug was only able to be tested in patients with severe cancer who could not be treated by other means. It was because no one knew whether the drug was really effective in advance. No early-stage patient was willing to be given such a drug. I thought it was natural that the drug failed to show efficacy because it was given to the patients for whom no drug would work. (Interview)

Another target was prostate cancer, which was a very common cancer in the US and in European countries. There was no very effective treatment for this cancer in the advanced stage. Surgical castration was effective but often caused psychological trauma. Oestrogen therapy was also effective but with considerable side effects. (Gittes 1991, 241-242) Therefore, the potential market seemed to be promising. The development of leuprorelin for this use was first conducted by TAP Pharmaceuticals, a joint venture between Takeda and Abbott, in the US, where there were a large number of patients with the disease. (Takeda 1983, p.743; Fujino 1992, p.8;

[8] Leuprorelin succeeded in obtaining an approval by the Japanese regulator for the treatment of pre-menopausal breast cancer in 1996, four years after its marketing for the treatment of prostate cancer in the country. (Takeda internal document)

Kuwashima 1996, p.122) Kunio Takeda, the then senior vice president of TAP Pharmaceuticals and a member of the Takeda family, championed the development of the drug. (Fujino interview) The drug for this application was then tested in animals (Warner, Santen, Demers and Max 1981) and in patients (E.g. Warner et al. 1982; Vance and Smith 1984; Santen et al. 1984; Smith et al. 1985). Comparative clinical trials with surgical castration or oestrogen therapy were also conducted. (Warner et al. 1983; The Leuprolide Study Group 1984; Winfield and Trachtenberg 1984) The drug went through clinical trials successfully and obtained an approval for the treatment of prostate cancer from the FDA in the US in 1985. It was marketed under the trade name "Lupron®" in the country. As mentioned in Section 6.3, the drug was at first given by daily injection, presupposing self-injection. (Fujino 1992, p. 8)

However, the development of leuprorelin in Japan was slower. First, there were fewer patients with prostate cancer in Japan. (Fujino interview) Second, because self-injection was not usually permitted in Japan, daily injection was difficult in practice there. (Yamanaka, Makino, Kumasaka and Shida 1984, 558; Fujino interview) Third, as a result of these, there was a strong suspicion about marketability of the drug in Japan amongst the management and the marketing division of Takada. Fujino described the situation:

> In Japan, prostate cancer was not common at all. So, nobody thought of [leuprorelin] seriously. They said, "This would not sell even 200 million yen at best." Only Konishi-san [the then president of the company] stood by us, saying that this should be developed in Japan as well. But the others disregarded the drug, which is now the best selling drug in Takeda. ... I think if Konishi-san had not supported it, it might have been abandoned. So, its development in Japan was late. ... In Japan, self-injection wasn't permitted except insulin. So, they said, "Daily injection can't sell in Japan. Who wants to go to the doctor everyday?" (Interview)

In this situation, researchers at Takeda sought a more convenient preparation. In the middle to late 1970s, Yasuaki Ogawa and his colleagues at the Pharmaceutics Laboratories of Takeda tried several preparations of leuprorelin such as a nasal spray, but failed to obtain stable absorption. Then, they turned back to injection, but this

time, they thought of a slow-release preparation by putting the drug into biodegradable microcapsules, so that the patient would need only one injection in a month, for example. Since the mid-1970s, a number of studies on using biodegradable materials for making slow-release preparation had been reported. However, most previous applications were for steroids, which were insoluble in water, and with tiny sticks of biodegradable polymer rather than microcapsules. Therefore, it was a difficult challenge for them to find out how to enclose the hydrophilic peptide in particles of hydrophobic biodegradable polymer with an even distribution. They chose a co-polymer of lactic acids and glycolic acids (PLGA), as the biodegradable material. Around 1975, Ogawa had heard of this material from Tai Matsuzawa, who was a senior researcher of the Pharmaceutics Laboratories and in the US at that time. (Ogawa interview[9]) Matsuzawa, one of the earliest experts in biological pharmaceutics in Japan, was sending new concepts and information related to the area, including bio-availability (BA) and drug delivery systems (DDS), from the United State to Japan. PLGA was part of that. This material was then well known as biodegradable and used in the United States, but the ratio of mixture was varied and needed optimisation. (Matsuzawa interview[10])

The first task for Ogawa's team was to obtain the polymer. This was not easy. Ogawa put it in detail:

> I asked various chemical companies in Japan for the polymer, but they said they didn't know about such material and didn't produce it. Then, I wrote to the American Company that had published a book about the material, asking for it. They said they could supply it, but the price was ten thousand dollars per 100 grams of the polymer. ... That was too expensive. So we gave up the idea of buying it and decided to make it, based on the patents. Because our company had a polymer group in the chemicals division, I went there first and asked. The man I asked was one of my peers employed in the same year and gave me an OK. However, when the plan went up to a higher rank, another man gave me a ring, asking, "How much do you want?" When I said, "Ten or twenty kilograms at most in a year," he said, "You should know that you need at least a ton if you want to order a chemical product. We can't do

[9] The interview with Dr Yasuaki Ogawa, who developed the depot preparation of leuprorelin, and Mr Kouji Sonoi, who was involved in the clinical development of leuprorelin, was conducted on 27th January 1999.
[10] The interview with Dr Tai Matsuzawa was conducted on 8th February 1999.

> business on such a small scale. I don't know what your friend said, but we can't help you."
> Then, we tried to synthesize the polymer by ourselves. But, it was impossible for us to make it, referring only to the patents. So, there was nothing left for us but to look for a chemical company who could make the polymer for us. ... Fortunately, Wako Pure Chemical Industries in Osaka, which was producing cellulose polymers for pharmaceutical uses, took it seriously and sent a researcher to our laboratories. The researcher happened to be a two year junior of mine in the same course at the same university. ... The company agreed to synthesize the polymer for us, and we were able to start the research at last. That was in 1980 or 1981. (Interview)

Ogawa's team at Takeda and researchers at Wako made a joint effort to obtain a suitable polymer for the purpose. First, they developed a method of polymerisation without using a heavy metal catalyst. This was because they were unable to get the material necessary for the conventional method using a heavy metal catalyst. At the same time, the new method was better than the conventional one because the former was free from contamination of the heavy metal. Next, they tried to optimise the average molecular weight and the ratio of the mixture of lactic acid and glycolic acid. They synthesized 7 or 8 polymers with different ratios of mixture and examined their biodegrading and drug releasing properties. The best ratio of lactic acid/glycolic acid for a month-long release was found to be 75/25. This work was completed in 1984. (Ogawa and Toguchi 1991, 22; Ogawa 1999)

In parallel with the development of the polymer, Ogawa and his colleagues also developed the method for producing microcapsules. First, they tried the method called the phase separation method, which Syntex patented for a LHRH analogue preparation in 1982. However, they did not have a powerful mixer and when they tried it with their less powerful one, they could not obtain proper microcapsules. Ogawa, an expert of emulsion research, next tried another method called the in-water drying method, which produced microcapsules from a threefold, water/oil/water emulsion of the drug. This method produced good microcapsules though the rate of capture of the drug was only 5%. By differentiating the viscosity of the inside water solution including the drug and the outside water solution and by doing the process under a very low temperature, they managed to improve the rate of capture up to more than 95% by the end of 1984. Luckily again for them, this method was later

found to be more suitable for mass production than the phase separation method used by Syntex and Schally's group, because it did not need an organic solvent, which was potentially dangerous and difficult to remove completely from the product. (Ogawa and Toguchi 1991, 20-21, 23; Ogawa interview; Ogawa, Okada, Heya and Shimamoto 1989)

The sustained-release preparations, or the depot preparations, of LHRH analogues, like the one developed by Ogawa's team, were also being developed by other groups, including ICI, Syntex and Schally's group around the same time. These groups were keenly competing with each other. All the mentioned groups adopted PLGA as the matrix material and all but the ICI group adopted microcapsules as the form. (Sanders et al. 1984; Redding, Schally, Tice and Meyers 1984; Hutchinson and Furr 1985) Takeda was not always the top runner. Ogawa wrote:

> I have experienced two serious shocks, which nearly made me quit the work. The first shock was the encounter with Syntex patent. ... Their idea was the same as ours, and we were far behind. We just managed to produce microcapsules on a small scale. Although I was deeply disappointed, my boss encouraged me to catch up with them before commercialisation. The second one was when I saw Dr Sanders' paper in the *Journal of Pharmaceutical Sciences* and Prof Schally's one in *Proceedings of the National Academy of Sciences* in October 1984. I supposed, at first, that they were in clinical trials, and my shock then was even bigger than the first one. However, when I collected more information about them, I found that both were using the same method, which was originally created by Southern Research Institute, and neither had yet been tried clinically. I was convinced that I could catch up with them before commercialisation because I knew that their method had problems. (Ogawa and Toguchi 1991, 23)

By using a different method, Ogawa's group was able to avoid existing patents and file their own patent. (Japanese Patent *Tokkai* 62-201816)

The next problem that Ogawa's team faced was to obtain the support of other divisions and the management of the company. Because the preparation was unfamiliar to everyone, there was a strong doubt within the organisation about whether the regulator and doctors would accept it. Ogawa put it:

> When I proposed this, 99% of people in the development division looked suspicious. "What price are you proposing to the government?" "How can doctors control the treatment?" "Do you think doctors will be willing to leave their patients alone for a month?" Most opinions were like that. Only one, the then director of the development division, Dr Takahashi supported us. Without him, this project might have been discarded. More accurately, only Dr Takahashi and Mr Konishi, the then president, said that this was very interesting. Of course, people in the research division, including Dr Morita, the then head of the division, supported us. But the rest in our company said that it would be hard to market such a drug. (Interview)

In 1984, the clinical development of the depot preparation managed to become a project, and was given a codename TAP-144-SR. At the beginning, its priority was still very low. However, when the company asked its allied overseas companies in the US and Europe which of its projects they found most interesting, all answers included TAP-144-SR. TAP Pharmaceuticals, which was about to launch the daily injection preparation of leuprorelin promptly announced that they would also develop the depot preparation in the US. Soon after that, European partners also decided to develop it in European countries. This movement enhanced the priority of its development in Japan. (Ogawa interview; Ogawa 1999)

In 1985, the depot preparation proceeded to clinical trials in Japan. However, there was another difficulty there. Kouji Sonoi, a manager at the Pharmaceutical Development Division of Takeda, said, "Doctors in Japan at first regarded the drug as out of the question. ... They were unfamiliar with the concept of a one-month-long acting drug." (Interview) Ogawa added, "It was also difficult to make the protocol for the clinical trials, because the drug was an unprecedented one." The protocol of clinical trials is usually made through discussion with a manufacturer of a new drug and doctors who conduct its trials. However, in the case of leuprorelin, doctors had no experience in clinical trials of this kind of drug. Here, it was fortunate for Takeda that the drug had already been marketed in the US with the preparation for daily injection, and that the clinical trials of its depot preparation also were more advanced in the US than in Japan. The experience in the US helped in the making of the protocol and reduced the anxiety of doctors about its efficacy and safety. (Ogawa and Sonoi, interview) The efficacy and the safety of the depot preparation were shown in clinical trials in various countries. (E.g. Sharifi, Soloway and the

Leuprolide Study Group 1990; O'Brien and Hibberd 1990; Giraud 1990; Akaza et al. 1990; Bischoff and German Leuprorelin Study Group 1990; Niijima et al. 1990; Rizzo et al. 1990; Aso et al. 1991)

There was a problem in the manufacturing of the drug, too: how to make sure of its germ-freeness. This was an essential task to pass the inspection of regulators. Because the drug was a peptide and contained in the delicate microcapsules, the easiest way, heating, was not available. Therefore, Takeda's engineers decided to make all the production processes germ-free. It was an extremely troublesome effort to construct the germ-freeness of all processes. They achieved this by showing that every element such as equipment and material was germ-free. It is reported that more than 1,000 documents were produced to validate the germ-freeness of each element of the production process. (Toguchi, Ogawa, Okada and Yamamoto 1991, 407; Ogawa and Fujino 1994, p.189; Ogawa interview)

The depot preparation of leuprorelin was first marketed in the US, France and Italy in 1989. The launch in Germany and the UK followed. In 1992, it was launched in Japan, as Leuplin®. (Ogawa 1999; Ogawa and Fujino 1994, p.190) Meanwhile, other applications, such as the treatment for endometriosis, precocious puberty and uterine fibroids, were also clinically studied (E.g. Dlugi, Miller, Knittle and Lupron Study Group 1990; Lee, Page and The Leuprolide Study Group 1989; Parker and Lee 1989; Friedman et al. 1991). These were approved by regulators later. (Ogawa 1999; Takeda internal documents) The sales of leuprorelin worldwide in 1994 were 425 million dollars. (Rickwood and Southworth 1995, p.119)

The success of the depot preparation of leuprorelin brought organisational power to pharmaceutics researchers, the researchers working on pharmaceutical system such as preparation and dosage forms, in Takeda. Ogawa explained it:

> Before, pharmaceutics researchers were regarded as only blenders. Preparation was not necessarily regarded as a research area in the research division. [Since the success of the depot preparation] everyone has recognized that preparation is a research area. The company founded the

> DDS Research Laboratories. They also built a new building for the Pharmaceutics Laboratories. (Interview)

The drug also enhanced the significance of pharmaceutics amongst academics and bureaucrats in Japan. Ogawa put it:

> I think that this was a major cause, though not the only cause, which made the concept of drug delivery system important in the Japanese society of pharmaceutical sciences. Leuplin is now ... recognized by academics as textbook stuff. Another thing is that the Ministry of Health and Welfare has recognized these products, maybe because [Leuplin] worked very well. They gave us quite a reasonable price for the drug. (Interview)

Sonoi added that the depot preparation of leuprorelin by injection contributed to establishing an advantageous differentiation of the product from the most significant rival product, goserelin, which adopted a different form of depot preparation and was marketed a little earlier than the leuprorelin depot preparation. (Sonoi interview)

6.5. Goserelin

The Pharmaceuticals Division of Imperial Chemical Industries (ICI) had a research tradition in sex hormone-related medicines for humans and animals. (Sneader 1985, pp.198-199; Furr interview) Tamoxifen citrate (Nolvadex®) was one of the products from this tradition. The drug, discovered by Arthur Walpole and his colleagues, was an effective anti-oestrogen and marketed for the treatment of breast cancer in 1973. (Sneader 1985, p.199; Kennedy 1993, pp.133-134, p.175) Walpole was also in collaboration with Geoffrey Harris at Oxford on research on LHRH from 1966. (Furr 1991; see Section 6.2) Barry Furr, one of the key researchers who discovered goserelin, described their position in the area at that time:

> ICI Pharmaceuticals worked with Harris, trying to isolate that factor. And at the time that Schally and Guillemin described their deca-peptide, ICI had three possible structures for LHRH. One of which was the same, two of which were different. So we were very close behind Schally and Guillemin. And this work was done by Arthur Walpole, Geoffrey Harris and an outstanding peptide/protein chemist called Harry Gregory. (Interview)

Furr succeeded Walpole in some of his responsibility in the reproductive biology unit at ICI's Pharmaceuticals Division in the mid-1970s. By that time, a number of research groups in the world had begun to synthesize and examine LHRH analogues to find a drug. ICI's team also started the search for effective LHRH analogues for pro-fertility and anti-cancer uses. Furr put it:

> Initially, we were looking for agents that were the same as LHRH but more potent and more stable, and our concept was that we could use these to stimulate reproduction. At the same time, we were looking for LHRH antagonists, and our view was that these would inhibit reproduction. And these were the ones that we believed to be useful in breast and prostate cancer and in sex hormone-dependent gynaecological conditions. So we had a concept that: LHRH agonists would be pro-fertility, and then LHRH antagonists would inhibit fertility. That was the overall view. (Interview)

Based on the information that replacement of amino acids at position 6 and at position 10 was important for obtaining the potency and the stability of LHRH analogues, Anand Dutta and his fellow chemists at ICI tried not only D-amino acids, as others were doing, but also α-aza-amino acids, whose derivatives were rather unexploited. This was because they thought that both types of amino acids were more resistant to peptide-destroying enzymes (Dutta and Morley 1975; Dutta and Giles 1976; Dutta, Furr and Hutchinson 1993, 11-12) Furr described the situation:

> When LHRH agonists were being developed, there was a recognition that they were rapidly broken down in blood and tissues by enzymes, and they were cleaved between positions 6 and 7, and 9 and 10. ...
> We tried primarily D-amino acids and aza-amino acids. And we tried then in various positions, we tried two azas, one aza in 6 and one in 10, we tried D-amino acid in 6 and aza in 10, and that was the combination that gave us the best results in terms of intrinsic potency, potency at the level of the pituitary gland and also stability from attack by the enzymes. (Interview)

ICI researchers also had to work outside the patents of other companies. However, this was not the starting point of their research. Again, Furr's explanation:

> We chose to put an aza-glycine in, which gave us, we believe, a better quality product. So there was an element of avoidance although at the time we were doing it, there was a lot of overlap, because other people were working at the

> same time. So we weren't always sure what other people were doing. It only became clear later. (Interview)

The ICI research team thus synthesized more than a hundred analogues. Among them the one that showed best total performance in terms of efficacy and duration of action was chosen to be developed in 1976.[11] This was goserelin, which substituted a D-amino acid, D-Serine (Bu^t), at position 6 and azaglycine at position 10 (fig. 6.1e). Goserelin showed 100 times higher ovulation-inducing activity in rats. (British Patent 1524747; Dutta, Furr, Giles and Valcaccia 1978; Dutta et al. 1978; Dutta, Furr, Giles and Morley 1976; Dutta, Furr and Giles 1979a; Dutta Furr and Giles 1979b; Dutta, Furr and Hutchinson 1993, 11-13; Furr 1998, 118; Furr interview)

When Furr and his colleagues examined goserelin, they encountered the paradoxical effect of LHRH analogues, as other researchers working on them did. (Dutta, Furr and Hutchinson 1993,13-15; Furr 1998, 119) Furr described it:

> We realized this was not a paradox but a well-known effect, which was described by physiologists as desensitisation of tissue, by pharmacologists as tachyphylaxis, and then by molecular biologists and by biochemists as receptor down-regulation, which was describing the mechanism of action. So it was a well-appreciated phenomenon. But because endocrinologists rather than pharmacologists worked on it, it was initially a surprise... (Interview)

When Furr noticed the paradoxical effect, he switched the target of goserelin to the one for LHRH antagonists, the treatment of sex hormone-dependent diseases such as breast cancer and prostate cancer. (Dutta, Furr and Hutchinson 1993, 15; Furr 1998, 119; Furr interview) The use for stimulating fertility was not impossible, but it required practitioners to administer the drug every 90 minutes. Furr thought that this could not be a major use. (Furr interview) Therefore, Furr and his colleagues investigated the possibility of using the drug for the treatment of breast cancer, which they were familiar with through the prior development of tamoxifen. They tested the drug in rats and found that it had an anti-tumour activity against a certain kind of mammary tumour. (Nicholson and Maynard 1979; Furr and Nicholson 1982)

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[11] According to Dr Furr, easiness of synthesis on a large scale may have been also taken into consideration. (Furr personal communication, July 2000)

However, there was a concern about the strategic positioning of goserelin when they already had tamoxifen citrate, an effective drug for the treatment of breast cancer. Furr put it:

> One of the problems I had ... was that we also had Nolvadex [tamoxifen], which was very good in breast cancer, and that was an orally available drug with a reasonable side effect profile. So, I was not clear how we could develop Zoladex [goserelin] to be commercially successful as a daily injection in breast cancer, when we had a good competitor, which was Nolvadex. It was in the same company but even if it had been in another company it would still have been a difficult competitor, to argue a case. (Interview)

Furr and his colleagues changed the primary target of goserelin to the treatment for advanced prostate cancer, which had a few alternative treatments such as surgical castration and oestrogen administration but all were not without problems, as mentioned above. (See Section 6.4.) They did not give up its use for the treatment of breast cancer, but the priority was put on the treatment of prostate cancer. (Furr interview) Clinical Studies of goserelin for the treatment of prostate cancer started in the early 1980s. Three early studies with about 10 patients claimed the efficacy of the drug in the treatment. (Allen et al. 1983; Walker et al. 1983; Ahmed et al. 1983) Another report claimed that the drug failed to show a long-term efficacy in the treatment of 15 patients. (Kerle, Williams, Ware and Bloom 1984) However, later studies with the depot preparation of goserelin did not support this report. The failure was interpreted as probably due to the variation of patients, based on a study with 29 patients (Grant et al. 1986, 542), or perhaps due to insufficient dosage and less than ideal preparation form, based on a study with 27 patients. (Murphy et al. 1987) Trials with a larger number of patients did not demonstrate the therapeutic failure again. (Debruyne et al. 1988; Peeling 1989; Soloway et al. 1991)

Meanwhile, a depot preparation of goserelin was developed. Although daily injection could be used and was used in the early studies, it was thought that the preparation would limit the acceptance of medical practitioners and reduce patient compliance with the treatment. They began to investigate alternative ways of administration of the drug. Nasal administration was examined, but they found that it was not suitable

because the absorption rate was low and too variable. The next preparation considered was a depot preparation with a biodegradable material. (Dutta, Furr and Hutchinson 1993, 15) Here, Furr's human network contributed to the solution. He explained it:

> I had some very good fortune with Zoladex in that I had worked with a formulation scientist, called Frank Hutchinson, and we together developed slow release formulations of prostaglandins for dogs. ... So I said, one day, to Frank, "We have an LHRH agonist, which is a peptide, and we need to deliver this as a monthly depot so that we don't have to give daily injection. And ideally, we want something that's biodegradable so that there will be no depot left at the end of the month. It's no good having to cut pieces of plastic out of a patient. Can you do it?" And he had the concept that he could by using polymers of lactic acid and glycolic acid. So, he said he could do it, and a lot of people said, "This would be impossible because how can you encapsulate a biodegradable peptide in a biodegradable matrix and expect to get activity?" But he had all sorts of reasons why he could do it. And he did it. And I tested the materials he made and they worked. (Interview)

Suspicion was not only about feasibility of such preparation but also about the absence of immune rejection response to the used material. (Furr 1998, 119) However, Hutchinson began to attack the target in 1979. (Furr interview) In the development process, a serendipitous event saved the project. Furr talked about the episode:

> [The preparation] seemed to work for a very short period, ... a period of about a week. But we couldn't ... get longer periods of action. Then, I went on holiday, and the person who was collecting the samples continued to collect them for a much longer period than we normally did. And when I came back, I analysed the results. What had happened was that we got our usual seven-days worth of activity, then we lost activity for between seven and twenty days, and then the activity returned. Frank Hutchinson then realized, when he saw these data, that there were two phases of release of the drug. ... He realized there was a diffusional phase of release, followed by a degradation phase of release. So, then he could change the characteristics of the polymer of lactide and glycolide to overlap diffusion and degradation, and then you got a smooth release of the drug. So, it was a bit of good fortune that I'd gone on holiday, because we might not have realised that there was a secondary phase, because normally we stopped the experiment when we lost the activity. (Interview)

The first depot preparation of an LHRH analogue, a tiny rod of PLGA matrix containing the drug for implanting, was thus developed in 1981. (Furr 1998, 119; Dutta, Furr and Hutchinson 1993, 15-21; Hutchinson and Furr 1985)

Soon, clinical trials of the depot preparation of goserelin started. In them the drug was compared with existing endocrinological treatments, surgical castration, oestrogen therapy and even the daily injection of the same drug. It was shown that the preparation was as effective as surgical castration and oestrogen, safer than oestrogen, and more effective than the daily injection of goserelin. (Grant et al. 1986; Van Cangh, Opsomer and Wese 1986; Namer et al. 1986; Murphy et al. 1987; Emtage et al. 1987; Peeling 1989; Soloway et al. 1991)

There were several problems to be solved in the process of clinical development. Firstly, ICI workers had to explain the mode of action to the medical and regulatory authorities because they expected that goserelin would have a stimulatory effect but it had an inhibitory effect. (Furr interview) Secondly, "super-active" LHRH analogues in fact had an acute stimulatory effect, often called the "flare-up" phenomenon. (Waxman et al. 1985) They were able to demonstrate that this phenomenon was not serious to patients unless they had an imminent risk of spinal collapse. (Furr interview; Grant et al. 1986, 542; Murphy et al. 1987, 189; Beacock et al. 1987, 440-441; Chrisp and Goa 1991, p.281) This phenomenon was observed in every "super-active" LHRH analogue, and it was proposed that the combination therapy with anti-androgens could avoid the exacerbation of symptoms caused by the phenomenon. (Labrie et al. 1984; Klign, De Voogt, Schröder and De Jong 1985; Gittes 1991, 242) Some other side effects also had to be explained and shown to be practically insignificant. Thirdly, establishment of its production was a very difficult task. The production of the peptide on a large scale with a high degree of quality and stability was another unprecedented achievement and required a lot of skills and effort. (Furr interview) These problems were resolved by organisational integration, in particular, through a multi-disciplinary team, consisting of chemists, biologists, pharmacists, pharmacologists, toxicologists, production managers and project coordinators. (Furr interview)

Goserelin was first launched in the UK in 1987 for the treatment of prostate cancer under the trade name "Zoladex®." It was then marketed in the US in 1990 and in Japan in 1991. Meanwhile, applications for the treatment of pre-menopausal breast cancer, endometriosis and fibroids were also clinically developed (Williams et al. 1986; Zeneca 1999a [breast cancer]; Shaw and Zoladex Endometriosis Study Team 1992; Candiani et al. 1990; Zeneca 1999b [endometriosis and fibroids]). Goserelin was launched in the UK for endometriosis and breast cancer in 1992 and for fibroids in 1996. (Furr personal communication, July 2000) The sales of goserelin worldwide were estimated to be 321 million dollars in 1994. (Rickwood and Southworth 1995, p.119)

6.6. Discussion

6.6.1. Uncertainty Surrounding Drugs

When we look through the case of LHRH analogues described above, we can see clearly how much and how different kinds of uncertainty there have been in the discovery and development of the drugs. Firstly, there was uncertainty about the molecular structure of LHRH. Secondly, there was uncertainty about how to improve potency and stability by modifying the structure of LHRH. Discussion about these two kinds of uncertainty seems to have been closed since the late 1970s. Thirdly, there has been uncertainty about how to use LHRH analogues. Fourthly, intertwined with this, there has been uncertainty about the mode of action of LHRH and its analogues. These two types of uncertainty were more observable in these drugs than in others in the previous chapters because they had the paradoxical effects, that is to say, the opposite effects to what were originally expected. The uncertainty about the action mechanism and the application opportunity is still high and open to discussion. It is important to note that the uncertainty has also been socially conditioned. For example, the pharmaceutical companies had to explore the mode of action of their drugs before they could explain the paradoxical effects.

There was also uncertainty related to the clinical development of LHRH analogues. Failures in their clinical trials clearly show us various aspects of the uncertainty around clinical trials. In the case of leuprorelin, the drug showed efficacy in rats with mammary tumours, but failed to show the same level of efficacy in patients with breast cancer. This may be due to the differences between rats and humans. It may be due to the differences of the stage of progress of the disease. Other explanations are also possible. In the case of goserelin, one of its clinical trials failed to show the long-term efficacy in prostate cancer, although the others showed that. This may be due to the shortage of its dosage. It may be due to the form of preparation. It may be due to the variation of the patients. Again, there are a lot of other possible explanations. Therefore, various factors, including the characteristics of the tests (E.g. *in vitro* or *in vivo*), the characteristics of the subject (E.g. rats or humans, males or females, early stage patients or advanced stage patients), the variety of the subject, the dosage of the drug and the form of the drug, consisted of the uncertainty around clinical trials. It should be noted, again, that these factors are also social ones. Availability of subjects, availability of types of the drugs and acceptability of experimental methods are all socially conditioned.

There was also uncertainty related to the manufacturing of the drugs. We can find various aspects of this uncertainty in the development of the depot preparation of leuprorelin. Difference between production in the laboratory and that in the plant was revealed. Supply of the material was also found to be uncertain. Patents by others limited the development. Tacit knowledge played an important role, because Takeda's researchers failed to reproduce the polymer from the patents only, but the polymer maker that helped the company managed to do that. Availability of equipment also limited the development of production methods. The optimisation of polymer and the improvement of microcapsules were achieved through a trial-and-error method. The validation of germ-freeness of the production process was made through a step-by-step way. All of these constituted the uncertainty surrounding manufacturing. It is obvious that they are socially conditioned. For example, a small quantity of organic solvent used in laboratories was not a problem, but a large quantity of it for commercial production would have required a special building,

special equipment and special expertise to control it, under regulations. This would have cost a lot and become a serious problem for the pharmaceutical company. This enhanced the company's preference for the method without organic solvent to the one using it. Therefore, the difference between production in laboratories and in plants was not only a "technical" issue but also a social issue.

Finally, there was a class of uncertainty which was more obviously social. One was organisational uncertainty. The leuprorelin researchers at Takeda faced suspicion amongst the management and the other divisions. But for the support of the then president, the product would have been discarded. The goserelin researchers faced a strategic problem when they considered the application for the treatment of breast cancer because they already had another potent drug in the same therapeutic area. There was also market uncertainty. The companies had to explain to the medical authorities and the regulatory authorities how their drugs worked, how effective they were and how safe they were. This market uncertainty was also the major source of the organisational uncertainty.

6.6.2. Types of Innovation

In the previous chapter, we identified two types of innovation in the pharmaceutical industry: paradigmatic innovation and modification-based innovation. The former was characterised by very high uncertainty, people's unfamiliarity with the drug and their suspicion, the necessity of strong leadership and the exemplary role of the drug. The latter was characterised by moderate scientific and technological uncertainty, the social restriction of modification, the importance of organisational integration and systematic resource mobilization, and the necessity of the construction of differences.

The innovation of LHRH analogues described in this chapter appears to be closer to paradigmatic innovation. There was high uncertainty as discussed above. People inside the organisation and outside were at first unfamiliar with the drugs and showed their suspicion. Strong leadership was needed. However, the exemplary role of the drug was not very clear. Various LHRH analogues were simultaneously

developed by different organisations. Leuprorelin was the first LHRH analogue with modifications at position 6 and 10. Goserelin was the first LHRH analogue with the depot preparation. Both played an exemplary role in a particular aspect among the class of drugs, but neither was an absolute exemplar. Various competing LHRH analogues affected the shaping process of each other. In such a situation, the construction of differences, one of the major characteristics of modification-based innovation, was important. Thus, various LHRH analogues collectively made a paradigm and were at the same time differentiated from each other. It can be said that in the case of LHRH analogues, paradigmatic innovation and modification-based innovation were mixed. This implies that the distinction between paradigmatic innovation and modification-based innovation is not a matter of a dichotomy but a matter of degree.

6.6.3. Competition and Innovation

In the case of LHRH analogues, it is noticeable that keen competition was observed throughout the innovation process: in the discovery of LHRH, in the synthesis of LHRH analogues, in the development of clinical applications, in the development of preparations and in clinical trials. Several groups in the US, Europe and Japan always participated in each stage of the competition, though there were a few cases of entrance and exit. On the one hand, this competition cost each player. It limited the potential range of choice in technology for each through a patent war. Patients for clinical trials are also limited. For example, it was reported that the introduction of the depot preparations of LHRH was delayed because of this limitation. (Waxman and Saini 1991, 419) However, on the other hand, the competition benefited the players. Each of them obtained information and ideas from the others through patents and papers. In addition, their efforts collectively educated medical professionals, patients and regulatory authorities so that these people could accept this class of drugs easily. It is difficult to say whether the beneficial aspects of the competition overwhelmed the costs for each player. However, it can be said that the competition accelerated the innovation process of LHRH analogues as a whole.

6.6.4 Cultural Factors in Innovation

It does not seem that there are remarkable differences between the case of leuprorelin and that of goserelin. However, it is doubtful whether Takeda would have succeeded in developing leuprorelin without its alliance with Abbott and the development of the drug in the US conducted by the alliance. As described, researchers at Abbott once collaborated with Schally. They possessed the *in vitro* assay, which Takeda did not have at that time, for LHRH and its analogues. This and probably some more technologies and skills were transferred from Abbott to Takeda, though some were also transferred from Takeda to Abbott. It was researchers at Abbott who discovered the paradoxical effects of leuprorelin and proposed the alternative application for the treatment of breast cancer and prostate cancer. It can be said that these are indicating the gap in quality and quantity of scientific expertises between the US and Japan at that time.

It was also said that without the precedent development of the drug in the US by TAP Pharmaceuticals, the joint venture between Takeda and Abbott, it would have been more difficult to develop it in Japan. There was difference in the number of patients with prostate cancer between the US and Japan. There was also difference in regulation between the two countries. For example, self-injection was permitted in the US but not in Japan. However, it seems difficult to attribute the delay of the development of leuprorelin to these only. The evaluation of the drug amongst managers, medical practitioners, patients and regulators in Japan seemed to be influenced significantly by the evaluation in the US. Probably, these people in Japan were more cautious with something uncertain than their American counterparts. It is likely that this risk-aversion of people in Japan also contributed to the delay of the development of leuprorelin in Japan, compared with the US and European countries.

In the next chapter, we examine three more cases of drug discovery and development in Japan in detail to confirm the different types of pharmaceutical innovation, which arose in this and previous chapters.

Chapter 7: Three Case Studies of Pharmaceutical Innovation in Japan

7.1. Introduction

In this chapter, we examine three cases of drug discovery and development, which took place in Japan, in order to confirm the existence of different types of drug innovation and to understand the properties of each. The first case is that of mevastatin, the first, exemplary drug among a class of drugs called HMG-CoA reductase inhibitors. Although this drug itself was not brought to market, it provides us with a rare case of paradigmatic innovation in Japan. The second case is cefotiam, a cephalosporin antibiotic, which can be regarded as a modification-based innovation. The third is the case of tamsulosin, a drug called an α_{1c}-blocker which is used for the treatment of urination disorder accompanying benign prostate hypertrophy. This drug is chemically one of the drugs called α-blockers, which had not been unfamiliar to experts, but it was the first one used for urination disorder. This drug, therefore, can be regarded as a modification-based innovation as a compound, but can be regarded as a paradigmatic innovation as a therapy. In each case, the detailed process of innovation inside the company is examined.

7.2. Mevastatin

7.2.1. Introduction

The drugs called HMG-CoA reductase inhibitors, including lovastatin, pravastatin and simvastatin, are used for the treatment of hypercholesterolemia. Hypercholesterolemia refers to the presence of abnormally large amount of cholesterol, especially LDL-cholesterol, in the circulating blood, and it may cause such diseases as arteriosclerosis and coronary heart disease. HMG-CoA reductase is the rate-limiting enzyme in the synthesis of cholesterol in the body. HMG-CoA reductase inhibitors antagonize the action of the enzyme and reduce the amount of

LDL-cholesterol in the blood. HMG-CoA reductase inhibitors appeared on the market in the late 1980s and have been remarkably successful. The sales of lovastatin (Mevacor®) and pravastatin (Mevalotin®) were estimated to be 1.3 and 1.6 billion dollars, respectively, in 1993. (Scrip Yearbook 1995, Vol. 1, p.102) Simvastatin (Zocor®) is more successful. Its worldwide sales had surpassed those of lovastatin by 1994 and amounted to 3.6 billion dollars in 1997. Simvastatin was probably the top selling drug in the world in the late 1990s. (Yakugyo Jihou 1999, p.131)

Lovastatin, pravastatin and simvastatin are all analogues of a drug, mevastatin (ML-236B; compactin), which was the first HMG-CoA reductase inhibitor discovered by Akira Endo at Sankyo Co. in Japan in 1973. However, the development of mevastatin was ceased in 1980. Meanwhile, Merck Co. (US) obtained experimental data and samples of mevastatin from Sankyo, discovered lovastatin in 1978, and marketed it in 1987. Merck also chemically synthesized simvastatin from lovastatin, and launched it in 1988. Sankyo re-examined analogues of mevastatin just after giving up the development of mevastatin, and decided to develop pravastatin, which had been already discovered by Sankyo's researchers in 1979. Pravastatin was launched in the market in 1989. In contrast with the enormous success of these analogue drugs, the story of the discovery and development of mevastatin, the prototype drug, was full of hardships. Although mevastatin failed to be a drug, its discoverer, Endo still believes that mevastatin could also have been as successful as its analogues if it had been marketed.

7.2.2. Mevastatin

Akira Endo was a senior researcher at the Fermentation Research Laboratories in Sankyo, the dedicated laboratories for the discovery of useful substances from microbes, when he started research on anti-cholesterol drugs in 1971. Before that, from 1966 to 1968, he had stayed in New York to study the biochemistry of phospholipid and cholesterol. (Endo interview[1]; Endo 2000) At that time, scientists were close to understanding the synthesizing process of cholesterol in the body

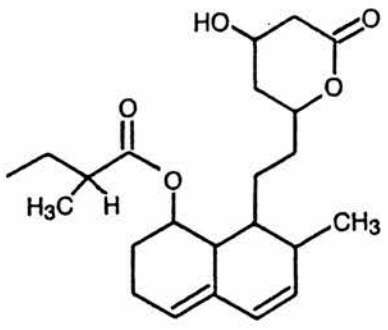
[1] The interview with Dr Akira Endo was conducted on 5th November 1999.

(Bloch 1965) and had identified HMG-CoA reductase as the enzyme that plays a central role in controlling the process. (Bucher, Overath and Lynen 1960; Siperstein and Fagan 1966; Siperstein 1970; Dietschy, Jean and Wilson 1970) The relationship between the amount of cholesterol in the blood and the frequency of coronary heart disease was also well known (the Framingham study). (Emerson Thomas et al. 1966; Dawber and Kannel 1966) People in the United States had become very conscious about the amount of fat in their diet because a great number of people there died of heart diseases, though this had not necessarily been the case in Japan yet at that time. However, there was no truly effective and safe anti-cholesterol drug even in the US. At first, Endo's interest was in the biochemistry of phospholipid and cholesterol, but later he became interested in the discovery of an anti-cholesterol drug, after learning about cholesterol-related diseases. (Endo interview)

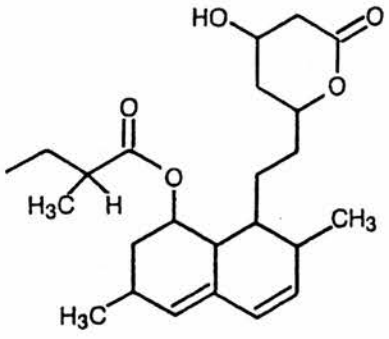
Table 7.1: Major Events Discussed in This Section

Year	Events
1971	Research Started
1973	Discovery of Mevastatin by Endo (Sankyo)
1974	Turndown of Mevastatin by the Central Research Laboratories
1976	Discovery of Mevastatin's Effectiveness in Hens Organisational Authorisation for Pre-clinical Study of Mevastatin
1977	Controversy on the Safety of Mevastatin in Sankyo
1978	Clinical Trials of Mevastatin by Yamamoto Organisational Authorisation for Clinical Development of Mevastatin Discovery of Lovastatin (Merck)
1979	Discovery of Pravastatin (Sankyo)
1980	Suspension of the Development of Mevastatin
1981	Organisational Authorisation for Development of Pravastatin
1984	Clinical Trials of Pravastatin Started
1987	Launch of Lovastatin (Merck)
1988	Launch of Simvastatin (Merck)
1989	Launch of Pravastatin (Sankyo)

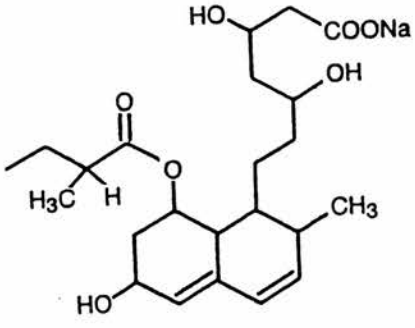
Figure 7.1: HMG-CoA Reductase Inhibitors discussed in This Section



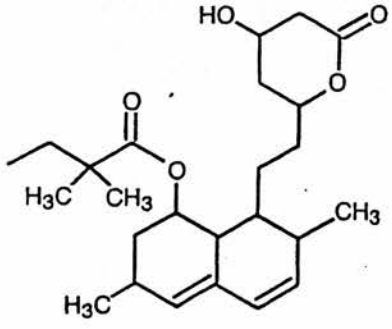
Mevastatin



Lovastatin



Pravastatin



Simvastatin

After coming back to Japan in autumn 1968, Endo was involved in research on antibiotics for a while. Simultaneously, he studied the literature on cholesterol to find a way to the discovery of an anti-cholesterol drug. Three approaches were considered for lowering the amount of cholesterol in the blood: blocking the intestinal absorption of cholesterol from the diet, inhibiting the synthesis of cholesterol in the body, and promoting its excretion. (Kuwashima 1998, p.461; Endo 1992, 1570) Inhibiting the biosynthesis seemed most effective of the three alternatives because biosynthesis was regarded as contributing most to the amount of cholesterol. (Siperstein 1970) Furthermore, he learned from the literature that the activity of HMG-CoA reductase is closely related to the overall rate of cholesterol synthesis. (Endo 1992; Siperstein and Fagan 1966; Siperstein 1970; Dietschy, Jean and Wilson 1970) By autumn 1970, he was convinced that he could reduce the amount of cholesterol in the blood if he could inhibit the activity of HMG-CoA reductase in some way. (Endo 1999) At the time, however, his idea was only a hypothesis without any "hard" evidence.

Endo, subsequently, decided to search for a substance able to inhibit HMG-CoA reductase from microbes, rather than from chemical syntheses. This choice was based on his interests and expertise. He was familiar with and interested in microbes, especially moulds and fungi, from his childhood in a farm family. He studied them at the Department of Agriculture, Touhoku University, and continued researching them to find useful substances for medicine and agriculture after he joined Sankyo. (Endo interview; Endo 1999) He also speculated that some microbes would produce HMG-CoA reductase inhibitors as a weapon to fight against other microbes that required sterols like cholesterol for growth. (Endo 1992, 1570) Since 1969, he had been at the Fermentation Research Laboratories, which was newly established to reinforce the search for antibiotics and other drugs from microbes. About 80 researchers at the laboratories were involved in the search for antibiotics. A half of the rest, about 10 researchers including Endo, was seeking drugs like various enzyme inhibitors. Therefore, he was in a position which was organizationally suited to him searching for HMG-CoA reductase inhibitors from microbes. (Endo interview; Kuwashima 1998, pp.460-461)

Endo, with Masao Kuroda, devised an assay system using rat liver enzymes to identify inhibitors of biosynthesis of cholesterol. A more specific assay system, which could detect only HMG-CoA reductase inhibitors by using [^{14}C] HMG-CoA, was also available, but it was too expensive to use for screening thousands of samples. The method they chose was less focused: it could not distinguish the inhibition of HMG-CoA reductase from any other inhibition in the early stages of the cholesterol synthetic pathway. (Endo 1992, 1570) However, the method was less expensive and so they could afford it. To obtain further savings, they improved the existing assay system and achieved 20 times to 40 times higher efficiency. (Endo 2000; Kuwashima 1998)

In April 1971, Endo and Kuroda began the screening of samples extracted from various microbes. For over 2 years, approximately 6,000 microbial strains were tested for their ability to inhibit cholesterol synthesis. As the result of the screening, two strains of moulds were found to produce active substances. One was *Pythium ultimum*, which produces citrinin, a substance known as a mycotoxin. However, they gave up the development of citrinin as an HMG-CoA reductase inhibitor because it was too toxic. (Endo interview; Endo 1992, 1570) The other was a strain of *Penicillium citrinum*, which produces mevastatin (formerly called ML-236B or compactin), ML-236A and ML-236C. Neither ML-236A nor ML-236C was so active as mevastatin. Mevastatin was discovered in July 1973 and its structure was determined by a combination of spectroscopic, chemical, and X-ray crystallographic methods three months later. (Endo, Kuroda and Tsujita 1976; Endo 1992, 1570) Later it was also identified that mevastatin is an HMG-CoA reductase inhibitor. (Endo, Kuroda and Tanzawa 1976) It took Endo more than two years, and came as he was reaching the limits of his patience:

> I was prepared to give up this approach if we were unable to gain a feeling of hit for two years. The feeling is that we will likely hit a target if we keep trying a little more. Without such readiness in mind, a search of drugs tends to get bogged down. This is unlike a lottery, which must includes prizes. [In a search of drug,] no one knows if there is a prize. ... It is like a battle, in which we have the limited variety of and the limited number of forces. If we have

> no prospects of victory after a two-year-long battle, we should retreat. (Endo interview)

In early 1974, Endo's team handed over mevastatin to the *in vivo* assay team at the Central Research Laboratories, where efficacy and safety of drugs are preliminarily tested in animals. (Endo 1992, 1573; Kuwashima 1998, 462) Mevastatin cleared acute safety tests, but, unexpectedly, it was found in March 1974 that the substance did not lower plasma cholesterol in rats. Rats were the predominantly used animals in the first stage of *in vivo* tests. Other animals such as rabbits, dogs and monkeys were occasionally used, but only after tests in rats because they were more expensive than rats. Rats were the first living "filter" for screening out inappropriate substances. Mevastatin was screened out there. (Endo interview; Endo 1992; Kuwashima 1998, 463)

Endo did not give up. Mevastatin was the product of his hard work for almost three years. Furthermore, he was not convinced that ineffectiveness in rats truly indicated ineffectiveness in humans. He and his team members decided to conduct *in vivo* tests by themselves. (Endo interview; Kuwashima 1998, 463) At the time, he belonged to the non-antibiotic research groups at the Fermentation Research Laboratories. This research institute was still a young organization and, in particular, the non-antibiotic research groups there were regarded as groups of "play," which were not expected to bring immediate products to the company. Therefore, his research proposal about anti-cholesterol drugs was readily approved when he submitted it to the director in April 1974. (Endo interview) Endo and his colleagues gave mevastatin to rats by injection and tried the substance in mice instead of rats, but failed to obtain any good results. The only hope was that the substance reduced the amount of cholesterol in the blood when they administrated it to the disease-model rats (that is, the rats artificially made hypercholesterolemia). (Endo 1987; Endo 1992, 1574) They also conjectured that the cholesterol inhibiting action of mevastatin could be antagonism against HMG-CoA reductase because of the structural similarity between an HMG-CoA molecule and a mevastatin molecule. This mechanism of action was in principle very suitable for a drug. (Endo interview; Endo 1992, 1571) However, their work continued for two years without good results. (Endo interview)

In the meantime, Endo learned of the work by Goldstein and Brown which showed that the activity of HMG-CoA reductase is suppressed by a particular class of lipoprotein known as LDL and that HMG-CoA reductase in cells from patients with familial hyper-cholesterolemia (FH) is not suppressed by LDL. Goldstein and Brown proposed the existence of LDL receptors and the deficiency of them in FH patients. (Brown, Dana and Goldstein 1973; Brown and Goldstein 1974)[2] Their studies of cholesterol metabolism strongly helped Endo's study in both experimental techniques and in the general idea of developing HMG-CoA reductase inhibitors. (Endo 1992, 1572) Endo wrote to Goldstein in October 1975. Endo's work interested Goldstein. Goldstein agreed with Endo's idea that mevastatin might work in disease cells. He also proposed to Endo that they conduct joint research. Endo acquired cells from FH patients from the United States and tested mevastatin in the cells and other mammalian cells by using the techniques Goldstein and Brown developed. As a result, he confirmed that mevastatin strongly inhibited synthesis of cholesterol in (cultured) human and other mammalian cells. (Endo 1992, 1572; Endo 1987; Endo 1991)

In early 1976, Endo decided that he should change the animals used in the experiments from rats to other animals with high levels of HMG-CoA reductase in their livers. When he happened to talk with a senior researcher at the Central Research Laboratories, who was doing the toxicity tests of agricultural chemicals with hens, he asked the researcher to try mevastatin in the hens that had been used in other experiments and were going to be killed. Endo thought hens were appropriate for trying mevastatin since the eggs they lay every day are rich in cholesterol. Because the talk between Endo and the researcher was an informal one in a bar, the idea was realized without any organizational resistance. Endo has speculated that the tests in hens might not have been realized if they had been formally proposed to the Central Research Laboratories, which had turned mevastatin down two years before. (Endo interview) The tests were conducted in spring 1976. Endo and his colleagues found that the amount of cholesterol in the hens was reduced by as much as 50%.

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[2] Goldstein and Brown won the Nobel Prize in 1985 for these achievements.

Because hens are not mammals, the data were not acceptable for drug development. However, the remarkable results in hens opened up an opportunity to conduct tests in dogs and monkeys. (Endo interview; Endo 1992, 1574) When they administrated mevastatin to dogs, the amount of cholesterol in the blood was reduced by 45%. Mevastatin also showed remarkable potency in monkeys. (Tsujita et al. 1979; Kuroda et al. 1979) Thus, Endo was convinced that mevastatin would be effective in humans even though it has no effect in rodents such as rats and mice. (Endo interview; Endo 1992, 1575) Sankyo decided to develop mevastatin as a drug in August 1976. It was also decided that the project would be a joint undertaking between the Fermentation Research Laboratories, the Central Research Laboratories and the Laboratory Animal Science and Testing Center, with Endo becoming the project leader. (Endo interview) Until then, Endo had experienced a lot of criticism in the company. He put it thus:

> There were a lot of [unpleasant] experiences. Some people said to me, for example, "Stop such research." Others said, "You waste young people," because I used several young researchers. Especially, our efforts probably made some people in the Central Research Laboratories irritated. You know, they were not happy, because they had turned [mevastatin] down but I tackled it persistently. ... At that time, the Central Research Laboratories was the centre of the drug development. Our Lab was only peripheral. (Interview)

An approach by Merck, the American pharmaceutical giant, to Sankyo about research collaboration on mevastatin possibly enhanced the value of the substance in the eyes of senior research managers at Sankyo. The patent of mevastatin was publicized in Belgium and Japan in December 1975. Having learned of this substance from the patents, Merck Sharp & Dohme Research Laboratories proposed some joint research to Sankyo on mevastatin in the spring of 1976. The two companies made a disclosure agreement, and Sankyo sent the related data, experimental methods and a sample of mevastatin to Merck. (Endo interview; Endo 1994; Endo 1987) Although Merck did not give an immediate positive valuation to mevastatin at that time (Endo 1994, 125), the company's approach drew the attention of the senior research managers at Sankyo to the substance.

Formal pre-clinical tests started in January 1977. In toxicological tests in rats, another problem arose in the spring of 1977. Toxicologists at the Laboratory Animal Science and Testing Center found tiny, unfamiliar crystals within the liver cells of the rats that were given a massive amount of mevastatin. They were very concerned about this phenomenon because mevastatin would be given to patients for a very long time. A subtle debate was held between Endo and the toxicologists. At that time, it was impossible for them to analyse the crystals directly. Using a variety of indirect evidence, Endo argued that the crystals were cholesterol ester, which should be resoluble. (Endo Interview; Endo 2000; Endo 1994, 124-125) The toxicologists and pathologists at the Laboratory Animal Science and Testing Center did not easily agree with him. Endo described the subtle character of the debate:

> When [the toxicologists] doubted the safety of a substance, its project would usually be abandoned. I have witnessed a lot of such cases. However, [the toxicologists] didn't used to say "no." It was because they didn't want to take the responsibility of stopping the project. They didn't want to incur our ill will. So, they asked us how we thought about the unfavourable results of their tests, instead of saying "no" straightforwardly. We answered it, but they were not convinced of our answer. We offered another answer, and so on. They just waited for us to give up the substance. This is a very Japanese way, isn't it? (Interview)

Endo also put it thus:

> It is a matter of course that unfamiliar phenomena are observed when we test an unfamiliar substance. [The crystal] was an example of such phenomena. Whether they can develop a unique drug or not is dependent on how they deal with such phenomena. I analysed the crystal and identified it as cholesterol. Even though I explained the phenomena logically, even though I showed evidence to the pathologists and toxicologists, they were not convinced. ... The story would have been completely different if there had been a precedent. If a company in America, Britain or elsewhere outside Japan had found the same thing and had insisted it's OK, there might have been no problem. (Interview)

About the same time, a group of chemists at the Central Research Laboratories was conducting synthesis of analogues of mevastatin. (Sato et al. 1979) They also tested biologically one of them, RWX-163 (R-163), without informing Endo's team. The first presentation about RWX-163 (R-163) in the company was given on 22 and 23

June 1977. In December 1977, the promoters of RWX-163 (R-163) insisted that the compound did not produce any crystals in liver cells of rats. They also claimed that it reduced the amount of cholesterol in rats. The proposal to replace mevastatin with RWX-163 (R-163) was discussed at the project-coordinating meeting on 10 January 1978. Unfortunately for Endo's team, Kou Arima, the then director of the Fermentation Research Laboratories and a main supporter of mevastatin project in the company, was absent from the meeting. The proposal won the consensus of the major members and was to be finally approved by Arima, who was also the director of the Central Research Laboratories. It was very hard for him to ignore the consensus at the meeting without convincing reason.[3] Mevastatin was thus about to be turned down again. (Endo interview and personal communication)[4] However, Endo and Arima did not give up mevastatin. Endo explained the reasons.

> The compound had only two hundred times less potency than mevastatin. This means patients would have to take it two hundred times more than mevastatin at a dose. Such a compound can't become a drug. However, for the chemists at the Central Research Laboratories, this was an opportunity for taking an initiative. Moreover, this was favourable for the pathologists and toxicologists at the Laboratory Animal Science and Testing Center because there would be no problem in their jurisdiction. Their interests coincided here. This resulted in one versus two. And, you know, it was the pathologists who were regarded as responsible finally for the safety of a substance. Therefore, if they didn't say "yes," a substance compound couldn't be a drug. (Interview)

Endo and Arima tried to find a way outside the company to save mevastatin from being dumped. Before then, in the autumn of 1977, Akira Yamamoto at the Osaka University Hospital had asked Endo for mevastatin to try it in one of his patients with serious familial hypercholesterolemia (FH). Yamamoto had come to know Endo through Endo's paper on the work of Goldstein and Brown. Yamamoto proposed that he would take the initiative with the tests. This was a genuinely attractive proposal for Endo. Soon after the project-coordinating meeting on 10 January 1978, Endo

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[3] Arima was somewhat regarded as an outsider in the research laboratories because he had worked at other department for a long time before he became the director. (Endo personal communication, April 2000)

[4] It should be noted that experimental results about mevastatin was presented in academic societies in 1977 but responses of scientists were not very favourable. Goldstein's team and Yamamoto's team were rare exceptions. (Endo 1987, 652; Endo 1994, 125)

went to see Yamamoto and arranged the tests. In Sankyo, only Endo and Arima knew of this plan.[5] The tests began on 2 February 1978. Arima later let the head of toxicology at Sankyo know about the plan of the tests. This caused turmoil within the organisation. However, there was no way for others in the company to stop the tests, because the doctor took the initiative. Doctors, especially ones belonging to universities, had great power over pharmaceutical companies at the time in Japan. At the next project-coordinating meeting on 9 February 1978, the direction shown at the last meeting was reversed and the development of mevastatin was approved. (Endo interview and personal communication)

The tests of mevastatin by Yamamoto's team at first did not show very good results. The amount of cholesterol in the blood was reduced but less than expected. Furthermore, side effects such as muscular weakness were observed. The tests were ceased. However, Yamamoto was intuitively convinced that mevastatin should work when he listened to the patient's neck and found that "vascular bruit (noise)" was impressively reduced after the use of the drug. The side effect was regarded as due to an overdose of the drug. In addition, the patients had a particular kind of hypercholesterolemia, called homozygous FH. Although his professor told him to give up the drug, he tried it again with alterations in dosages and targets. (Yamamoto 1999, 78) Yamamoto treated 9 other patients with primary hypercholesterolemia with lower dosage of mevastatin. These tests produced remarkable results. (Yamamoto, Sudo and Endo 1980; Endo 1992, 1575; Endo 1994, 125) In May 1978, the development of mevastatin was formally authorized at the corporate meeting of Sankyo head quarter. In November of the year, formal clinical trials (Phase I) began. However, Endo left Sankyo and moved to Tokyo Noko University in December 1978. (Endo 2000)

In the summer of 1979, clinical trials of mevastatin proceeded to Phase II and the drug was administrated to many patients with serious hypercholesterolemia by over

[5] Before the tests in Japan, Endo had planned the similar attempt in the US, based on a proposal of Goldstein to try mevastatin in his patients with serious FH in May 1977. However, this attempt was not realized because of the lack of sufficient safety tests and objection of a domestic medical authority. (Endo interview; Endo 1991, 721)

10 groups in Japan. The results showed that mevastatin was effective for all kinds of hypercholesterolemia except homozygous FH. Some of the results of clinical trials were presented at the International Symposium on Drugs Affecting Lipid Metabolism in June 1980. (Endo 1994, 126) However, most of these clinical trials were suddenly suspended soon after that symposium, because of the report that mevastatin showed toxic effects in some dogs at high doses in a long-term toxicity study. (Endo 1992, 1575) Endo criticised the study thus:

> [The tests] committed three errors. First, doses were too much. About 1000 times higher doses than the effective doses in man were given to the dogs. Second, a long-term toxicity study usually lasts for a year. However, in this case, it was extended to two years because there had been nothing wrong after 39-week-long administration. I can't understand why they made such a decision. ... Third, it was a matter of course that toxicity was observed. But the dose was 1000 times higher. They should have analysed the phenomenon logically, because there was nothing wrong in 50 times higher doses. Any drug would show toxicity if it was taken to the amount of 1000 times higher than ordinary doses. Therefore, such tests are total nonsense. (Interview)[6]

When Endo was at the company, he insisted that the long-term toxicity tests should be done with 50 times higher than the effective doses in human.[7] However, his insistence was not accepted. The much higher doses were adopted together with lower doses. It was because even the highest doses had not produced serious toxic effects in the middle-term toxicity tests conducted before. There was also an opinion that toxicity tests should be conducted with doses high enough to produce some toxic effects. (Endo 1991, 721) Endo generalized the problem here thus:

> If there had been an exemplar, it would have been all right. If an American company or a company elsewhere had done [a long-term toxicity study] with only 50 times higher doses, the Japanese company would have done with 50 times higher. But there was no such exemplar. [Mevastatin] was very safe. They thought that's OK because they didn't find toxic effects in the sub-acute toxicity tests [with the same amount of doses]. So easy. Their thinking wasn't based on theories. Very intuitive. I think this is a Japanese way of thinking. They are not good at thinking logically and analytically. (Interview)

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[6] About the details of the doses of the tests, see Endo (1992), 1575 and Endo (1994), 126.

[7] Even the doses Endo had insisted at that time were later found to be 250 times higher than the ordinarily effective doses. (Endo correspondence)

Although the results of the test might have been different if they had chosen lower doses and a shorter period of time, which was a practical option at the first trial, these sorts of experiment cannot be redone. Even if the second trial had showed that mevastatin had been safe, doubts among people could not have been wiped out completely. (Endo 1991, 721-722) As a result, Sankyo virtually ceased the development of mavastatin in the summer of 1980. Sankyo mentions this incident just briefly in its official story of mevastatin and pravastatin: "[pravastatin] was selected because of its advantage in the balance of efficacy and safety." (Sankyo, 1996, 10) Although mevastatin failed to be a drug, it was used in some medical studies even after that. In August 1981, Hiroshi Mabuchi and his colleagues at Kanazawa University reported effectiveness of mevastatin in 7 patients with FH. (Mabuchi et al. 1981) The team also reported in March 1983 that mevastatin was very effective in combination with another drug for the treatment of FH without any side effects. (Mabuchi et al. 1983) Yamamoto's team confirmed these results. These studies appeared to greatly accelerate the development of HMG-CoA reductase inhibitors in the 1980s. (Endo 1992,1576; Brown and Goldstein 1981, 516) Mevastatin provided "hard" evidence to support theories of cholesterol synthesis in the body. Brown and Goldstein acknowledged the contribution of mevastatin in the editorial of a major medical journal as following:

> Many hurdles must be overcome before compactin [mevastatin] and mevinolin [lovastatin] can be accepted as a "penicillin" for hypercholesterolemia. ... Yet, the studies with the parent compounds compactin and mevinolin have established a general principle: interference with cholesterol synthesis can trigger an increase in LDL receptors, thereby reducing LDL levels in plasma without depleting vital body stores of cholesterol. This is indeed encouraging news. (Brown and Goldstein 1981, 517)

7.2.3. Lovastatin, Simvastatin and Pravastatin: The Offspring

7.2.3.1. Discovery and Development of Lovastatin and Simvastatin by Merck

Merck obtained a sample of mevastatin and unpublished data related to it from Sankyo under a disclosure agreement in July 1976. According to Endo, researchers at

Merck appeared to be disappointed because of the poor results in rats. However, after Sankyo provided them with new data for dogs in October 1976, Merck became more interested in the research of mevastatin. In April 1977, Merck asked Sankyo for additional samples of mevastatin for tests. Endo taught researchers at Merck methods for experiments in dogs. By October 1978, researchers at Merck had reproduced the same experimental results as Sankyo's ones. (Endo 1994, 125; Endo 1992, 1576) However, the contract between Merck and Sankyo included a clause about maintaining secrecy, but did not include one about prohibiting Merck from conducting improved inventions for a fixed period. (Endo interview) Rather, the contract included a following clause:

> It is understood that no patent right or license is hereby granted to either party by this agreement and that the disclosure of proprietary information and materials shall not result in any obligation to grant either party any rights in and to the subject matter of the party. (Endo 2000)

Researchers at Merck began their own screening tests and discovered lovastatin from a strain of mould in November 1978. (Alberts et al. 1980; Alberts 1988; Endo 1994, 125)[8] It is reported that clinical trials of lovastatin were once interrupted because of the suspension of the development of mevastatin. However, Merck gradually resumed the clinical trials after the studies by Yamamoto and by Mabuchi which indicated the effectiveness of mevastatin for the treatment of FH. (Endo 2000; Endo 1994, 126-127) As to the survival of the project, the fact that the then president of the Merck Sharp and Dohme Research Laboratories, P. Roy Vagelos was a famous researcher in the biochemistry of lipids and cholesterol should be noted here. (Galambos and Sewell 1995, 125; Endo 2000) Lovastatin cleared clinical trials and was approved by the FDA in the autumn of 1987. (Hoeg et al. 1986; The Lovastatin Study Group II 1986; Havel et al. 1987; Grundy 1988, 25) In the course of clinical trials of lovastatin, the detailed action mechanism of HMG-CoA reductase inhibitors

[8] Endo independently discovered lovastatin from another mould in early 1979 and named it monacolin K. (Endo 1979; Brown and Goldstein 1981, 516) The application for patents of Monacolin K by Endo was before that of lovastatin, but because of the difference of principle in the US patent law and its counterparts of the most countries in the world including Japan (priority on invention versus priority on application), the patent of lovastatin became valid in the US only and the patent of monacolin K, which was handed over to Sankyo by Endo, became valid in the rest of the world. Therefore, Merck did not market lovastatin in Japan but did simvastatin later. (Endo 2000; Endo 1987, 652)

was explained. (Bilheimer et al. 1983; Grundy 1988) Side effects which occurred in animal tests at very high dosage levels were also successfully explained and did not inhibit the project. (MacDonald et al. 1988) In the early 1980s, Merck synthesized simvastatin by modifying lovastatin chemically. (Hoffman et al. 1986) The company developed it in parallel with lovastatin. In 1988, Merck marketed simvastatin, which became the second HMG-CoA reductase inhibitor marketed. (Todd and Goa 1990, 586-587)

7.2.3.2. Discovery and Development of Pravastatin by Sankyo

In parallel with the development of mevastatin, researchers at Sankyo had searched for a better HMG-CoA reductase inhibitor by screening natural substances and synthesized compounds. This work linked with the investigation of the mechanism, activities and the structure-activity relationship of mevastatin. That is, in order to understand mevastatin, it was necessary to examine related substances and compounds as well. Masao Kuroda, who was one of main researchers involved in the HMG-CoA reductase inhibitor project at the Fermentation Research Laboratories, described this process thus:

> In real laboratories, things don't proceed so neatly as "We have established the assay system. Now, let's begin the screening with it." In reality, we are building an assay system with trials and errors. (Interview)[9]

One of the substances discovered to be active in these efforts was pravastatin. This substance was first found in 1979 when Sankyo researchers examined the metabolites in the urine of dogs that were given mevastatin. (Kuroda interview; Serizawa et al.1983a, 604; Sankyo 1996, 10) Although the substance was found to be active when it was first discovered, the researchers could not identify its chemical structure because the quantity was too small. Because it was a metabolite, the researchers speculated that it should be a hydroxyl derivative of mevastatin. They tried to produce it by chemical modification and microbial transformation. The latter approach was found to be more efficient. Then, they matched the physical chemistry

[9] Interview with Dr Masao Kuroda was conducted on 24th March 2000.

properties of the substance thus produced with those of the metabolite and at last identified the structure of the substance named pravastatin. It was in fact a hydroxyl derivative of mevastatin. Establishment of large-scale production was also essential for them to conduct various pre-clinical tests and clinical trials. However, pravastatin did not become the candidate for the development immediately after the discovery but many other substances were examined as well. (Kuroda interview; Kuroda 1994, 76-77; Serizawa et al. 1983a; Serizawa et al. 1983b; Serizawa et al. 1983c; Serizawa et al. 1983d)

Soon after the failure of the development of mevastatin in the summer of 1980, Sankyo's researchers began reviewing "hundreds of" these analogues of mevastatin. (Kuroda interview; Kuwashima 1998, 463) The standard of potency was mevastatin. The new candidate substance had to be better than mevastatin. Pravastatin was the survivor of the screening. Kuroda described the situation at that time thus:

> The problem was that we were the first to develop an HMG-CoA reductase inhibitor in the world. In such case, there were objections and scepticism that such mechanism of action would not result in a drug. It was our pride as the first research team who discovered such kind of compounds that persistently led us to the development of pravastatin. (Interview)

Despite some voices of suspicion within the company, Sankyo decided to develop pravastatin in 1981. (Kuroda personal communication, April 2000; Kuwashima 1998) Sankyo stated that the choice was made because of stronger effectiveness and less toxicity. (Sankyo 1996, 10) The company attributed these advantages to the tissue-selectivity (that is, the ability to inhibit cholesterol synthesis selectively in livers and intestines) of pravastatin. (Tsujita et al. 1986; Koga et al. 1990; Sankyo 1996, 10; Tsujita 1993, 627-629) Researchers at Sankyo also made a considerable effort to develop a more efficient microbiological production method of pravastatin and succeeded in obtaining one using a strain of an Australian microbe. (Serizawa et al. 1983a; Serizawa et al. 1983c; Matsuoka et al. 1989; Sankyo 1996, 10) Clinical trials of pravastatin in Japan started in February 1984. Pravastatin cleared clinical trials rapidly with good results, (Nakaya et al. 1987; Mabuchi et al. 1987; Kuroda 1994, 82-83) and was approved for manufacturing by the Ministry of Health and

Welfare and marketed in Japan in 1989. It also went through clinical trials in the US and European countries and obtained favourable results. (Hunninghake et al. 1990; Hoogerbrugge et al. 1990) By 1996, it was being sold in 69 countries. (Kuwashima 1998)

The remarkable successes of these three analogues of mevastatin, namely, lovastatin, simvastatin and pravastatin, in the market were already stated in the introduction of this section. There are three other HMG-CoA reductase inhibitors marketed today, which are also highly successful in the market: atorvastatin (Lipitor®) marketed by Warner and Lambert, cerivastatin (Lipobay®) marketed by Bayer, and fluvastatin (Lescol®) marketed by Novartis. Although these three compounds share the key structure with mevastatin, they are less similar to mevastatin than lovastatin, simvastatin or pravastatin.

7.3. Cefotiam

7.3.1. Introduction

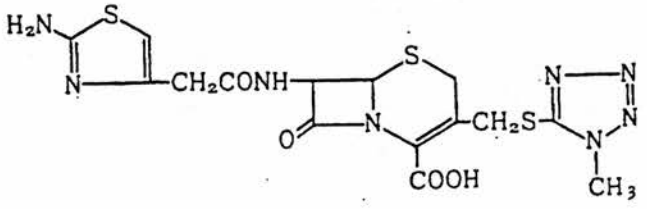
Cefotiam is an antibiotic synthesized and developed by Takeda Chemical Industries in Japan. This drug is classified into a subgroup of antibiotics called cephalosporins. Cephalosporins are analogues of cephalosporin C, originated in Italy but identified and investigated in the UK. Cephalosporins have the similar chemical structure to penicillins: both subgroups of antibiotics possess the structure called β-lactam. Therefore, they are also broadly called β-lactam antibiotics together with some other antibiotics with the same structure. Cefotiam was synthesized in 1974 (Takeda 1983, p. 743) and launched in Japan in 1981. Cefotiam is classified as one of so-called second-generation cephalosporins, which have broader spectrum of activity than first-generation ones, but in general lesser antibacterial activity against Gram-negative bacteria than third-generation ones. (Webber and Wheeler 1982, p. 377; Donowitz and Mandell 1988, 490) However, this does not mean the second-generation cephalosporins became obsolete after the advent of third-generation ones. This is because doctors do not always use the third-generation cephalosporins for

fear of making bacteria resistant to antibiotics. In Japan, the increase of antibiotic-resistant bacteria has been a major medical problem since the 1980s. (Hiramatsu 1999, 114) Narrower spectrum of activity has an advantage of preventing a broad range of bacteria from becoming antibiotic-resistant unnecessarily. (Silver and Bostian 1993, 378) Therefore, cefotiam has been sold very well in Japan even after the advent of third-generation cephalosporins. Its sales in Japan were estimated to be about 22 billion yen (about 110 million pounds) in 1998. It was the second best selling antibiotic for injection use in Japan. (*Yakuji Handobukku* 1999)

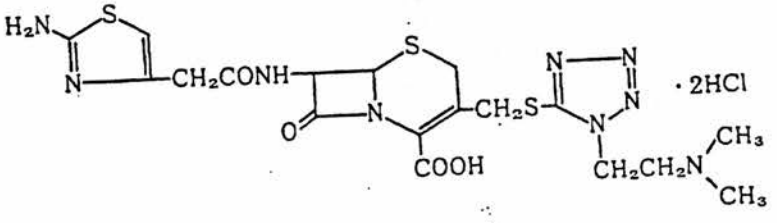
Table 7.2: Major Events Discussed in This Section

Year	Events
1945	Discovery of *Cephalosporium acremonium*
1953	Discovery of Cephalosporin C
1962	Synthesis of the first marketed cephalosporin, cephalothin
1971	Start of the cephalosporin project at Takeda
1974	Synthesis of SCE-785 and SCE-963
1975	Stop of the development of SCE-785; Start of the development of SCE-963
1976	Start of the clinical trials of SCE-963 (cefotiam)
1980	Approval for manufacturing of cefotiam
1981	Market launch of cefotiam

Figure 7.2: Cephalosporins Discussed in This Section



SCE-785



SCE-963
(Cefotiam)

7.3.2. Discovery and Early Progress of Cephalosporins

Giuseppe Brotzu, a professor at the Institute of Hygiene of Cagliari in Italy conjectured that self-purification of seawater might be partly due to microbial antagonism. In 1945, he sampled seawater near a local sewage outfall and discovered a species of mould, *Cephalosporium acremonium*, which produced a substance having a wider antibacterial activity than penicillin. He published his finding in a pamphlet in 1948, which had only a small circulation. This attracted little attention in the country. He then sent a copy to his friend in London, Blyth Brooke and suggested that English researchers should take up the work to isolate the active substances, which would be beyond his resources. Based on the suggestion of the Medical Research Council, Brook wrote to (Sir) Howard Florey at the Sir William Dunn School of Pathology at Oxford. Florey gladly agreed to take up further investigation. Brotzu sent a culture of his mould to Florey in September 1948. (Abraham and Loder 1972, pp.3-5; Selwyn 1980, pp. 39-40)

At Oxford, Edward Abraham and H. S. Burton found an antibiotic, named cephalosporin P, from the organic solvent extract of the Brotzu's culture by 1949, but this had only a narrow spectrum of antibacterial activity. In August 1949, they found another substance from the culture fluids. The substance, which was hydrophilic and had a broader spectrum of activity as described by Brotzu, was at first named cephalosporin N. This was later renamed penicillin N because it had the same nucleus of molecular structure as penicillin. In the process of isolating cephalosporin N, Abraham and G. G. F. Newton found the third antibiotic as a contaminant from crude cephalosporin N preparations in 1953. This substance, named cephalosporin C, was found to have similar range of activity to cephalosporin N but be much less active. However, this new antibiotic had some unique properties such as non-toxicity, stability and, in particular, resistance to penicillinase, a class of enzymes produced by bacteria. These enzymes destroy penicillins including cephalosporin N. (Newton and Abraham 1955; Newton and Abraham 1956; Abraham and Loder 1972, pp. 5-7; Sneader 1985, pp. 316-317)

The production of cephalosporin C in quantity was difficult at the time. The Oxford researchers helped the Medical Research Council's Antibiotic Research Station to produce the substance on a larger scale. The National Research Development Corporation (NRDC) secured patents related to the production of Cephalosporin C. (Abraham and Loder 1972, pp. 7-9; Selwyn 1980, p. 46) The Antibiotic Research Station had been founded to avoid repeating the situation that had arisen when British companies had to pay large royalties to produce penicillin by deep fermentation processes, which were developed in the US. NRDC had been established in 1949 to exploit discoveries made in Britain, which had, again, not been achieved in the case of penicillin. (Sneader 1985, pp. 316-317) NRDC asked all British pharmaceutical companies having fermentation facilities to help the production of cephalosporin C, but only Glaxo showed serious interest. In 1956, NRDC began to organize meetings between Glaxo and the researchers at Oxford and the Antibiotic Research Station. By 1957, 100mg of cephalosporin had been produced by Glaxo, some of which contributed to the work to confirm the chemical structure of the substance. (Abraham and Loder 1972, p.10)

Several foreign companies contacted NRDC and signed licensing agreements related to cephalosporin C with the corporation: Squibb and Eli Lilly in the US in 1959; Merck, Pfizer, SmithKline and French (all in the US), Ciba (Switzerland) and Farmitalia (Italy) in 1960; and Fujisawa in Japan in 1961. However, the possibility of developing cephalosporin C itself as a drug in practice disappeared when methicillin, a potent semi-synthetic penicillin, showed resistance to penicillinase in 1960. (Abraham and Loder 1972, p.10) Fortunately, the patient research on cephalosporins at Oxford, which was supported by the accumulation of intellectual and material assets obtained from their research on penicillin since the mid 1930s, provided cephalosporins with a future. By 1960, the researchers at Oxford had identified the chemical structure of cephalosporin C (Abraham and Newton 1961; Hodgkin and Maslen 1961), and found that 7-aminocephalosporanic acid (7-ACA), which could be obtained in small amounts from cephalosporin C by using a particular method, was a rich source of derivatives that had much higher potency than cephalosporin C. (Loder, Newton and Abraham 1961; Abraham and Loder 1972, p. 9, pp.11-15;

Selwyn 1980, p. 46) This meant, in principle, that it should be possible to produce a lot of potent semi-synthetic cephalosporins from 7-ACA in the same way as semi-synthetic penicillins were then being obtained from 6-aminopenicillamic acid. (Sneader 1985, p.318) The critical problem to exploit the commercial potential of cephalosporins was to discover a method for producing 7-ACA on a large scale. (Abraham and Loder 1972, pp. 10-11)

In 1960, Robert Morin and his colleagues at the Lilly Research Laboratories devised a more efficient procedure of converting cephalosporin C into 7-ACA. (Morin et al. 1962; Abraham and Loder 1972, p. 11; Selwyn 1980, p. 47) By that time, both Eli Lilly and Glaxo had achieved large-scale production of cephalosporin C by fermentation. Thus, 7-ACA became available in larger quantity, and a number of derivatives were synthesized and examined in search of potent antibiotics. At Eli Lilly, Robert Chauvette and his colleagues prepared a series of 7-ACA derivatives, and cephalothin was selected for clinical trials from them. (Chauvette et al. 1962) This was marketed in 1964 and became the first marketed cephalosporin. (Griffith and Black 1964; Selwyn 1980, p.47) Shortly after that, Glaxo also succeeded in making a marketable semi-synthetic cephalosporin, cephaloridine, which was marketed in 1964. (Muggleton, O'Callaghan and Stevens 1964; Selwyn 1980, p.47) Both cephalothin and cephaloridine were claimed to have a broader spectrum of activity than penicillins, to be active against some penicillin-resistant bacteria, and to be free from serious side effects. Safety to patients with penicillin allergy was also reported. (Griffith and Black 1964; Muggleton and O'Callaghan 1967) Eli Lilly, then, synthesized the first orally active cephalosporin, cephaloglycin, by adopting the same side-chain as ampicillin, a semi-synthetic penicillin developed by Beecham a little earlier. Shortly later, however, this drug was replaced by a better-absorbed oral cephalosporin named cephalexin, which was synthesized independently by Eli Lilly and Glaxo and marketed in 1967. (Wick 1967; Newall 1985, p.215; Selwyn 1980, p. 47; Sneader 1985, pp.318-319) In 1970, Chauvette and his colleagues at Eli Lilly developed a new chemical process for converting penicillin into cephalexin. This production process could be applied to other cephalosporins, and made the production of 7-ACA more efficient. (Chauvette et al. 1971; Selwyn 1980, p.47) By

1971, several cephalosporins with similar properties became clinically available, including cefazolin (Fujisawa), cephapirin (Bristol), and cephacetrile (Ciba-Geigy). (Hewitt 1973; Numata 1981, p.19) These cephalosporins were later called first-generation cephalosporins, which were more active against Gram-positive bacteria such as staphylococci and streptococci (non-resistant ones), but less active[10] against Gram-negative bacteria such as *E. coli*, *Klebsiellia* and *Pr. mirabilis*, than second-generation cephalosporins such as cefamandol, cefaclor (Eli Lilly) and cefuroxime (Glaxo), which were marketed since around 1972. (Donowitz and Mandell 1988; Numata 1981, pp.41-45) Cefotiam developed by Takeda was one of the second-generation cephalosporins. When they started research on cephalosporins in 1970, first-generation cephalosporins were their exemplars and targets to be superseded in the search for a new drug. (Numata 1981, p. 20)

7.3.3. Takeda's Start of Research on Cephalosporin

Takeda Chemical Industries is one of the oldest pharmaceutical companies in Japan, and also has decades of history of pharmaceutical research, including prodrugs of vitamin B_1 (Arinamin®) which had been major products of the company for a long time. (Morita 2000, pp. 173-175) In the 1960s and 1970s, antibiotics became the leading drugs which brought substantial profits into pharmaceutical companies in Japan. (Nihon Yakusi Gakkai 1995, pp. 119-123) In this area, however, Takeda did not have competitive products until the end of the 1960s. In 1967 Takeda started research on semi-synthetic penicillin and succeeded in synthesizing sulbenicillin disodium by 1968, which was marketed in 1973 (Lilacillin®). (Takeda 1983, pp. 755-756) The company also started preliminary research on cephalosporins in 1967. In order to discover a new cephalosporin, however, they had to establish the supply of 7-ACA, which was not generally available. In November 1970, Takeda agreed with Ciba-Geigy about cooperation on cephalosporin research. Under this agreement, Takeda started intensive research on cephalosporins with 7-ACA supplied by Ciba-Geigy in 1971. Results of the research would be shared between both companies. (Takeda 1983, p.743, p.764) Takeda also started research on production of

[10] First-generation cephalosporins were in general more active against Gram-negative bacteria than penicillins. (Hewett 1973, S314)

cephalosporin C in 1970. This research resulted in the invention of a new production process of deacetylcephalosporin C (DCPC) in 1973, which was later found to be able to be used as an alternative material for production of cephalosporins. (Takeda 1983, p.765) The sales force of Takeda, however, could not just wait for the birth of their new cephalosporin. Immediately after the agreement with Ciba-Geigy, Takeda developed a new production process for cephalexin, and marketed its generic product in 1973 under the process patent system in Japan.[11] In addition, Takeda and Ciba-Geigy cooperated on clinical trials and marketing of Ciba's cephalosporin, cephacetrile, in Japan. This was marketed in Japan in 1978. (Takeda 1983, p.818)

The earliest attempt at synthesizing a new cephalosporin at Takeda was conducted by the research group that had created sulbenicillin disodium, a semi-synthetic penicillin. In May 1970, they began to synthesize new cephalosporins on a small scale, having the agreement with Ciba-Geigy in prospect. They found that one of them, SCE-20, which had the same side chain as sulbenicillin disodium, had an activity against a particular group of Gram-negative bacteria called *Pseudomonas aeruginosa*.[12] This interested the researchers because existing antibiotics were hardly active against these bacteria. In 1971, with a supply of 7-ACA from Ciba-Geigy, they synthesized further analogues of SCE-20, and found that two of them, SCE-120 and SCE-129, were much more active against the bacteria than SCE-20 though they were not very active against other bacteria. Although there was doubt about its marketability, Takeda decided to develop SCE-129 in 1973 because of its unique activity against *Pseudomonas aeruginosa*. Researchers at Ciba-Geigy and academic specialists in infectious disease supported Takeda's decision. (Takeda 1983, p.971; Numata 1981, pp.11-16) SCE-129 was named cefsulodin and launched in 1981 (Takesulin®). From the beginning, however, it was obvious that this would not cover the needs of the sales division of the company, because of the narrow range of antibacterial activity of the drug. They needed a cephalosporin with a much broader range of activity.

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[11] Japan's patent system was reformed to be the product patent system in 1976. See Howells and Neary (1995), pp. 145-149.

[12] *Pseudomonas aeruginosa* are typical opportunistic pathogen and can cause various infectious diseases, including sepsis, osteomyelitis, airways infection, and urinary tract infection, particularly in patients who do not have a normal level of immunity. They are resistant to commonly used antiseptics and antibiotics and may cause hospital infection.

(Hiramatsu interview[13]) Although these early attempts did not earn much income, it should be noted that they earned trust from Ciba-Geigy and ensured further supply of 7-ACA, which helped further cephalosporin research at Takeda. (Takeda 1983, p. 971) The research group that produced cefsulodin did not belong to the Central Research Division, but to the Manufacturing Division. They were somewhat peripheral as researchers in Takeda. (Numata interview) The search for a broader cephalosporin, which the company truly needed, was conducted by the "mainstream" of Takeda's research division. (Takeda 1983, p. 973)

7.3.4. Discovery of Cefotiam

Takeda charged the First Chemical Research Department at the Central Research Division led by Katsura Morita with doing research to discover a new cephalosporin in 1971. Morita described this project as "a life-betting gambling" for the company and for himself. The project was created by strategic needs of the company, and the project team had to achieve the goal though they had no experience in synthesizing cephalosporins. If they failed, they would have had to take responsibility for the failure, and the company would have lost out in the Japanese antibiotic market. (Morita interview[14]; Morita 2000, pp. 207-208) Two of the staff of the Investigation Department also participated in the project team. They investigated almost all related patents and literature, and mapped the situation of cephalosporin research in the world, including chemical structures and antibacterial properties of all cephalosporins available. Pessimistic opinions arose in the team, when they looked at the chart. (Morita interview: Morita 2000, pp. 208-209) Morita persuaded his team members:

> I said, "There were only several thousand compounds. Despite this, no existing cephalosporin had stronger activity [against Gram-positive bacteria] than penicillins. In addition, penicillins were cheaper than cephalosporins. So, we can catch up [with leading companies]. Moreover, penicillin has only one

[13] The interview with Dr Mitsuo Numata, who was the leader of the key research group in the synthesis of cefotiam, Dr Kenji Okonogi, who was involved in the biological study on cefotiam and other antibiotics, and Mr Nobuyoshi Hiramatsu, who was involved in the development of antibiotics at Takeda, was conducted on 26th January 1999.

[14] This interview with Dr Katsura Morita was conducted on 8th February 1999.

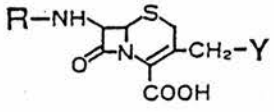
> place to be modified. But cephalosporin has two places. That means hundreds of thousands of compounds in principle can be synthesized. Not the level of several thousand. So, we have a chance." (Interview)

Morita succeeded in persuading his members. He also faced the question of which approach to adopt, random searching or rational searching. He thought about his available resources and chose the latter. He put it:

> It was a divergence whether was better: to make as many compounds as possible without thinking until coming across a hit, like blind shooting; or to make a working hypothesis first, then begin to synthesize compounds based on the hypothesis. I was afraid we would not tolerate the former choice. I thought we should make a hypothesis about why cephalosporins were active, what kind of mechanism killed bacteria, and what structure should be designed. The hypothesis had to be unique which others did not share. I thought we should make such a hypothesis by ourselves. My staff agreed with me. (Interview)

The hypothesis was made based on knowledge in organic chemistry in the related area (E.g. Sweet and Dahl 1970) and investigation of structure-activity relationship of existing cephalosporins. Morita and his colleagues conjectured that an "active hydrogen" in the side chain at 7 position of a cephalosporin molecule (figure 7.3) was linked with antibacterial activity of the drug by enhancing the chemical reactivity of the molecule to the cell-wall-making enzyme of bacteria. (Morita et al. 1980, pp. 17-18; Morita 2000, p. 209-212; Morita interview) Not all team members were fully convinced of the hypothesis. A few researchers did not adhere to the hypothesis. (Morita interview) It is still unclear if the hypothesis is correct. (Numata interview) Most researchers were, however, convinced that they would work with this hypothesis. Based on this hypothesis, they considered putting a particular atomic group called β-ketoacid into the side chain in order to produce an "active hydrogen" (figure 7.4). This structure was chosen because it was unique and not enclosed by patents of other companies. (Numata 1981, p.22: Morita et al. 1980, p.17; Numata interview) However, it was clear that this was a very hard task because β-ketoacid was very unstable. (Morita 2000, pp.212-213; Numata 1981 p.26)

Figure 7.3: First Generation Cephalosporins and the "Active Hydrogen"



R is called 7 position side chain.
Y is called 3 position side chain.
Ⓗ shows an "active hydrogen."

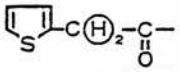
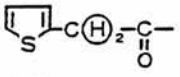
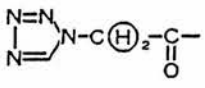
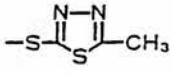
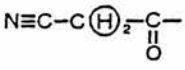
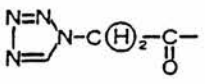
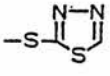
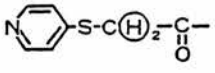
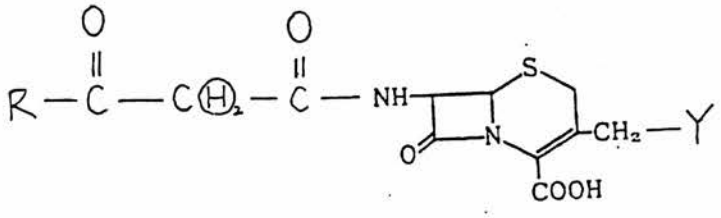
Generic Name	R	Y	Company
Cephalothin		$-OCOCH_3$	Lilly
Cephaloridine			Glaxo
Cefazolin			Fujisawa
Cefacetrile		$-OCOCH_3$	Ciba
Ceftezole			Fujisawa
Cephapirin		$-OCOCH_3$	Bristol

Figure 7.4: Target Compounds with the β-Ketoacid Side Chain

R and Y are variable chemical groups.
Ⓗ shows an "active hydrogen."



Morita thought that this project had to be done in at most three years. (Morita 2000, p.208) Morita organized five dedicated research groups. This was an exceptionally concentrated deployment of research force. Three of them were charged with chemical synthesis. One was in charge of pharmacological study. The other one was in charge of supply of β-ketoacids. (Morita interview; Numata interview) Morita mixed "lay researchers," that is, researchers who had not been specialized in the area, into the research groups. Morita put it:

> "Cephalosporins are more expensive than penicillins." "Cephalosporins are less active than penicillins." People who were familiar with antibiotics and penicillins tended to say such words to me. I did not want those people in my project team. I preferred ignorant people without such prejudice. Ignorant people can act boldly, take drastic measures and find something unexpected. ... Indeed, after all, they did produce excellent results. (Interview)

Mitsuo Numata, the leader of the winning research group in this project was one of the "lay researchers." He also share the opinion with Morita:

> [A success point is] that [Morita] did not use specialists only, but mixed lay people with specialists. ... If the team members had been specialists only, their view would have been much narrower. The team needed someone with foolishness enough to challenge what specialists believed to be impossible. Of course, lay people only would not have produced any better results. Mixture was important. (Interview)

There was keen competition between the research groups. Numata, one of the group leaders, and Kenji Okonogi, who conducted biological study of the compounds synthesized by all research groups, described the situation at that time merrily:

> **Hara:** Was there exchange of information between the research groups?
> **Numata:** No. Rarely. Because we were fighting each other (laugh). Members of each group spoke ill of other groups at Okonogi's laboratory. He was a good listener.
> **Okonogi:** Yes. I can confess it now. To be honest, it was a very hard job to be fair to every group (laugh).
> **Numata:** I asked him, for example, not to give this information to Dr Ochiai (laugh). All of us had a strong sense of rivalry. However, Morita had an ability to control this situation. (Interview)

Morita made careful efforts to control conflicts inside his research organization. He described an example of his efforts:

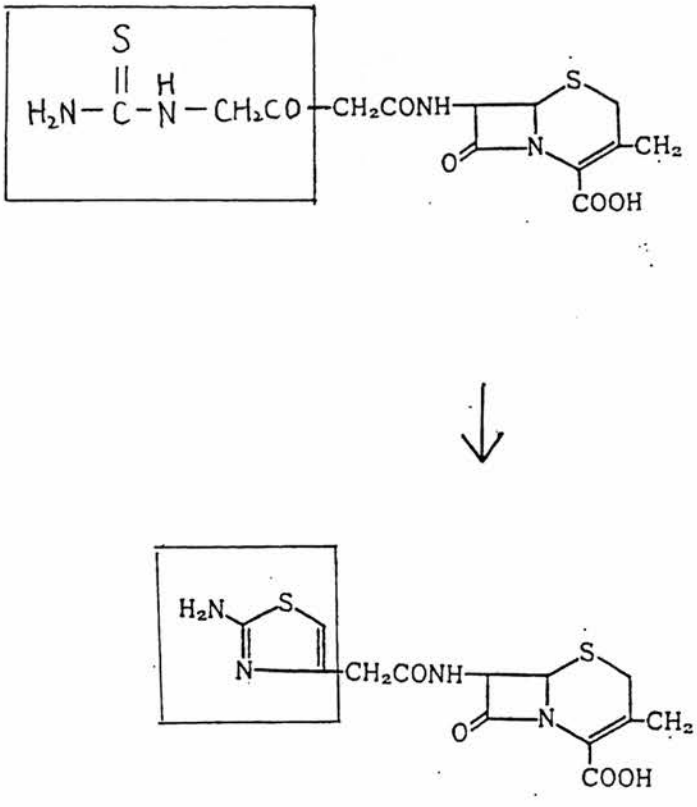
> I did not become a co-author of papers produced by the researchers in my department after I became the Head. I even declined to be mentioned in acknowledgements. ... If I had allowed them to put my name into their papers, I could not have promoted competition in my organization. If I had become a co-author of one research group, I would have had to become a co-author of another research group, in order to be neutral between them. But if I had done this, it would have made me look indifferent and somewhat irresponsible. (Interview)

In the first year of the project, SCE-150, which did not include β-ketoacids in the structure, was synthesized by one of the research group. Although SCE-150 was as potent as the most potent cephalosporin available at that time, Morita gave up its development because he believed that it would become obsolete before it appeared on the market several years later. (Morita interview)

The research group led by Numata succeeded in putting β-ketoacids into cephalosporin molecules at the 7 position side chain and synthesized many compounds. Most of them showed only disappointing activity. However, when they introduced an atom group called methyl-thio-methyl to the β-ketoacid side chain, the resultant compound showed fairly high potency. (Numata et al. 1978a, b; Numata 1981, pp. 25-26; Morita et al. 1983, p.19) This result encouraged them to make further analogues of this compound. Serendipitous discovery occurred in this process. When they tried to combine another related atom group called thiocyanate with the side chain, the nuclear magnetic resonance analyser in their laboratories was broken. Because of this, the compound was left for a week. After the machine was repaired, a young researcher of the group analysed the compound and found that it was different from what they expected. They examined the unknown compound and found that the atomic group at the end of the side chain had become a cyclic structure. Moreover, this new compound possessed a remarkable antibacterial activity, which was stronger than any existing cephalosporin, particularly against Gram-negative bacteria. This showed the way to what they were looking for. When they used thiourea, another related chemical group, in place of thiocyanate, the similar reaction, namely

"cyclization" occurred immediately and produced a cephalosporin with a unique side chain called 2-aminothiazol-4-ylacetyl in good yields (Figure 7.5). They then made an effort to optimise another side chain at 3 position. The consequent cephalosporin, codenamed SCE-785 (figure 7.2), satisfied the requirements for a competitive cephalosporin in the future market. Takeda decided to develop SCE-785 in July 1974, five months after its synthesis. (Numata et al. 1978c, 1262-1263; Numata 1981, pp. 27-30; Morita et al. 1983, p. 19; Takeda 1983, p. 973; Numata interview) The unique structure of SCE-785, 2-aminothiazol-4-yl, later became a standard component structure: most third-generation cephalosporins developed later adopted it. (Takeda 1983, p. 973; Webber and Wheeler 1982, p. 379, pp. 389-390)

Figure 7.5: The "Cyclization" of the β-Ketoacid Side Chain Resulting in Formation of 2-Aminothiazol-4-ylacetyl Side Chain



SCE-785 was pre-clinically tested for about a year. Its efficacy was confirmed. (Takeda 1983, p. 973) However, tiny deposits were observed in the kidney and the

bladder of rabbits to which a lot of SCE-785 was administrated. This was believed to be due to the low solubility of the compound in water. Morita insisted the continuation of its development because results in humans might be different from those in rabbits, but toxicologists at Takeda argued that they should wait for a better drug. (Morita 2000, p. 214; Morita interview) SCE-785 proceeded to clinical trials with healthy volunteers, but one of them showed side effects. This was also believed to be due to the low solubility of the compound in water. (Numata interview; Takeda 1983, p. 973) Thus, the development of SCE-785 was stopped in December 1975. (Takeda 1983, p. 973)

Along with the development of SCE-785, the search for a better cephalosporin was continued in Morita's department. This time, Morita concentrated researchers' efforts on improvement of 2-aminothiazol-4-ylacetyl cephalosporins, that is to say, analogues of SCE-785. (Morita 2000, p.213; Morita interview) At this stage, he made Numata's group open their information to other researchers in order to promote competition among them. (Morita interview) Numata was transferred to the manufacturing division to help development of the production process of SCE-785. (Numata interview) At Morita's department, further efforts were made to optimise the side chain at 3 position. Okonogi, who was involved in assaying of these compounds, described how busy he was at that time, to deal with the compounds synthesized one after another:

> We examined about 30 compounds a week. We divided them into two sessions. It took three days to assay compounds: plant bacteria on the first day; put compounds into the culture next day; then observe results on the third day. By that time, our company had adopted a five-day working week. ...So we had two sessions: Monday to Wednesday and Wednesday to Friday. We continued this for weeks. (Interview)

As a result, one hundred and fifty four compounds were synthesized. When the development of SCE-785 was stopped, several compounds having higher solubility in water were chosen from the newly synthesized compounds. After detail examination of these compounds, Takeda decided to develop one of them, SCE-963, in place of SCE-785 in December 1975. This compound, named cefotiam (figure 7.2),

also had a broad range of activity and was in particular more active against some of Gram-negative bacteria than existing antibiotics at that time. Cefotiam quickly passed through pre-clinical tests and proceeded into clinical trials in August 1976. (Takeda 1983, p. 973-974; Numata et al. 1978c; Morita et al. 1983, pp. 19-20; Tsuchiya et al. 1978)

7.3.5. Development of Cefotiam

Development of an efficient production process for cephalosporins proceeded concurrently with chemical syntheses and biological studies of the compounds. (Takeda 1983, p. 973) Production costs of cephalosporins had been a critical problem for the commercialisation of the drugs. Penicillins were much cheaper than cephalosporins at that time, and this produced obstacles to research and development of cephalosporins. Morita faced such criticism when he led the cephalosporin project at Takeda. He put it:

> One of my senior colleagues asked me, "Morita, I heard you began to research cephalosporins. But, do you know prices of penicillins and cephalosporins?" I said, "I don't know exactly, but cephalosporins seem expensive." He said, "10 times expensive. I mean, costs of raw materials. In addition, penicillins are fast in fermentation. Moreover, it is easy to extract penicillins into butanol, but cephalosporins are hydrophilic and insoluble in butanol. How could you succeed?" (Interview)

In order to reduce costs of cephalosporins, Takeda had made efforts early on in their cephalosporin research. As I mentioned above, they developed a new production process of deacetylcephalosporin C (DCPC) in 1973. They then invented a new route to produce semi-synthetic cephalosporins such as cefotiam from DCPC in good yields and on a large scale. This reduced production costs to an acceptable level. (Takeda 1983, p.974; Tsushima et al. 1979) It should be noted, however, that this problem of costs of cephalosporins was also related to patents secured by other companies. Numata explained it:

> At that time, only members of the syndicate [organized by NRDC] could use [the raw material, 7-ACA]. ... When we thought about methods of its

> production, we found more patents protected them. So, only DCPC enabled us to circumvent those patents. ... So, we at first made DCPC and use it as raw material of cephalosporins. Later, those patents expired one by one, and it became more economical to use 7-ACA available on the market than to use DCPC made by us. (Numata interview)

Takeda also had to design a unique preparation to make cefotiam suitable for practical use. Because of the production route of cefotiam and in order to maintain stability of the compound, the company decided to market cefotiam as a salt with two moles of hydrochloric acid. When this salt alone was dissolved in water, however, the solution was too acidic to be appropriate in clinical use. Therefore, they prepared sodium carbonate with the drug to neutralise the acid. Then, they reduced the pressure of phials containing the preparation to control carbon dioxide generated when water was added into the phial. To produce the phial, they also had to develop new equipment for packaging. (Takeda 1983, p. 974) Fortunately for them, however, the good solubility of the prescription was highly appreciated by medical practitioners including doctors and nurses, according to Nobuyoshi Hiramatsu, who was involved in the marketing of cefotiam. (Interview) This is because medical practitioners often face cases in which they have to administer an antibiotic to patients immediately. (Numata personal communication, June 2000)

Clinical trials of cefotiam went ahead smoothly. In February 1977, cefotiam proceeded to Phase II. Its double-blind trials with cefazolin, a highly potent first-generation cephalosporin developed in Japan, were conducted from November 1977. The results of these Phase III trials were presented at the annual conference of the Japan Society of Chemotherapy in June 1978. Efficacy and safety of cefotiam were supported there. (Shimizu, Kumada and Okuzumi 1979; Various papers in *Chemotherapy*, Volume 27, Supplement 3, April 1979) Based on these data, Takeda and its development partner Ciba-Geigy (Japan) obtained approval for manufacturing cefotiam from the Ministry of Health and Welfare in 1980. Takeda launched cefotiam under the trademark Pansporin® in February 1981. (Takeda 1983, p. 974)

Cefotiam was also marketed in several foreign countries including Germany, but its sales abroad were limited.[15]

Two institutional factors contributed to the relatively rapid development of cefotiam in Japan. First, because antibiotics were used for the cure of acute diseases, its long-term side effects were regarded as less important than those of drugs for chronic diseases such as hypertension and hypercholesterolemia. Rather, the regulatory body sought to approve any better antibiotic as soon as possible. (Hiramatsu interview) Second, there was a well-organized society of specialist doctors in the chemotherapy area in Japan. This society, the Japan Society of Chemotherapy was practice-oriented rather than basic-research-oriented: it focused on evaluation of drugs rather than research about infectious diseases. (The Japan Society of Chemotherapy, website[16]) This society had its own routine to manage clinical trials. When pharmaceutical companies asked the society to do clinical trials, it organized and arranged them. Then, the clinical trials proceeded steadily under the initiative of the society. This system strongly promoted development of antibiotics in Japan. (Hiramatsu interview)

Cefotiam was profitable because it was more active against bacteria than existing drugs at that time. This was not only because the drug was sold better than other drugs, but also because its price was fixed at higher level than other drugs by the regulatory body. In Japan, the official price of a drug is fixed in comparison with those of other equivalent drugs or most similar drugs if there is no equivalent drug. Because cefotiam was almost double as active as existing drugs, it succeeded in gaining the same price as others in only a half quantity. In other words, it won almost double price per gram, compared with existing drugs. (Hiramatsu interview)

[15] It was said that Ciba-Geigy gave up its launch in Switzerland because of its small sales prospects. In the US, its launch was not fulfilled because the delay of obtaining an approval from the regulatory body eroded its competitiveness. (Okonogi personal communication, June 2000)
[16] www03.u-page.so-net.ne.jp/jc4/karyo/index.htm

7.4. Tamsulosin

7.4.1. Introduction

Tamsulosin is a drug that is a remedy for the urination disorder accompanying benign prostatic hypertrophy. (Japanese Patent WO 95/02419, 1995) It was discovered by a research team led by Toichi Takenaka in 1980 at first as a potential anti-hypertension drug. However, its new application in the urological area of the drug was later recognised and it was clinically developed in this area. In addition, the drug was developed at first in its racemic mixture (Yamanouchi 1994; Takenaka, et al. 1995), that is to say, in a 50:50 mixture of two stereoisomers that have a mirror-image relationship. A racemic mixture is symbolized as (±), while each of the stereoisomers is expressed as (+) or (-). It was later switched to be the single (-)-isomer only. Tamsulosin (Harnal®) was marketed in Japan in 1993 (Yamanouchi 1994), in European countries in 1995 and in the US in 1997. (Takenaka interview)[17] It had sales in Japan of about 150 million pounds and its overseas sales were about 50 million pounds in 1997. (Nihon Sougou Kenkyusyo 1998, p. 274)

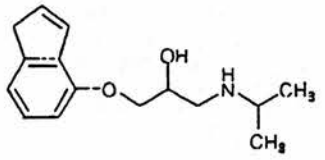
Table: 7.3: Major Events Discussed in This Section

Year	Events
1976	Research Started
1980	Discovery of YM12617 (a racemic mixture of tamsulosin)
1982	Organisational Authorisation
1983	Clinical Trials Started
1986	Switch to the Single (-) Isomers (tamsulosin)
1993	Launch in Japan

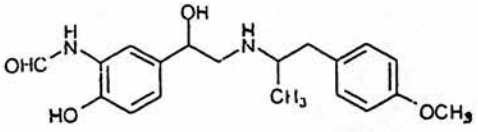
[17] The interview with Dr Toichi Takenaka was conducted on 22 January 1999.

Figure 7.6: Tamsulosin and Relevant Compounds

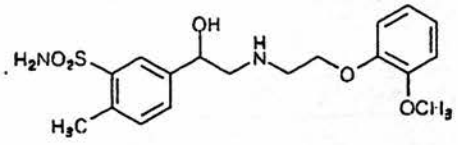
Indenolol
(YB-2)
Pulsan®



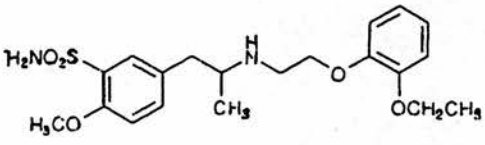
Formotelol
(YM-08316)
Atock®



Amosulalol
(YM-09538)
Lowgan®



Tamsulosin
(YM617)
Harnal®



7.4.2. Synthesis of Tamsulosin

Benign prostatic hypertrophy (BPH) often arises when men age. It causes some difficulties in urination such as retarded urination, frequent urination and residual urine. It is said that a fifth of men over 55 years old suffer from the disease. (Yamanouchi 1994) Although it is not a fatal disease, it seriously damages the quality of life of the patients. BPH had previously been treated by traditional Chinese medicine or hormone preparations. Surgery was the only treatment that was more effective. Furthermore, most patients were unwilling to go to urogenital clinics, partly because of the negative images of the clinics, especially in Japan, and partly because the disease was not fatal. (Takenaka interview) It was common for sufferers to buy over-the-counter (OTC) drugs based on traditional Chinese medicine to relieve the difficulty.

Tamsulosin was not synthesized at first as a drug for the treatment of the urination disorder. Researchers at Yamanouchi had been involved in research on α and β adrenergic receptors since 1965. As outcomes of this research, they discovered a β-blocker for the treatment of heart diseases and hypertension, indenolol in 1968, a β-stimulant for the treatment of asthma, formoterol in 1972, and an α β-blocker for the treatment of hypertension, amosulalol in 1976. (Yamanouchi 1994; Takenaka, et al. 1995) The discovery of tamsulosin stemmed from the research on amosulalol.[18] From the research on differences in the receptor selectivity of various α β-blockers, researchers found the (+)-isomer of amosulalol to be more potent in blocking α_1 receptors, a subtype of α receptors, and the (-)-isomer to be more potent in blocking β_1 receptors, a subtype of β receptors. They synthesized the derivatives of amosulalol to obtain more-potent α_1 blockers without β_1 blocking activity. They found that sulfamoylphenethylamines constituted a structurally new type of potent α_1 blockers. YM-12617 (the racemic mixture of tamsulosin), synthesized in 1980, was found to be the most potent compound of all (Takenaka, et al. 1984; Takenaka, et al.

[18] The research on tamsulosin was a continuation of the research on amosulalol. Therefore, it is almost impossible to identify the starting point on the research of tamsulosin. In this paper, I will define the starting point as being 1976, just after the discovery of amosulalol. See Fukai (1995), p.489.

1995) and became a candidate to be developed. (Figure 7.6) Therefore, tamsulosin was synthesized as an α_1 blocker, without a specific application of the compound. Toichi Takenaka explained why he turned his attention to α_1 blockers:

> I was interested in α receptors, because at that time a new theory emerged that there were two subtypes of α receptors, namely, α_1 receptors and α_2 receptors. Then, I was keen to know what kinds of roles each subtype played. So, we examined their distribution and related properties. I remained in this area of research because of my intellectual curiosity, and expected to lead studies and experiments, such as one on which subtypes govern the prostate and the urethra, to academic publication. (Interview)

The synthesis of the compound, in other words the modification from amosulalol to the compound, was said to have been done quite rationally and relatively smoothly. Takenaka put it thus:

> The drug design went smoothly, because the lead compound was our own and we had experience of amosulalol. And in our own research, we had been involved in research on the sympathetic nerve system for a long time, since around 1965. So, we had already, in our company, developed concepts, methods for experiments and whatever related to the drug. (Interview)

7.4.3. Discovery of the Application

At first, α_1 blockers were considered for use in treating anti-hypertension. However, Yamanouchi had already developed indenolol, nicardipine (Ca^{++} blocker) and amosulalol as anti-hypertension drugs and intra-company competition between these drugs existed. Therefore, the researchers started a search for an application of the new α_1 blocker. (Yamanouchi 1994)

The research team turned their attention to the area of urology. There were at least three reasons for this. First, they considered the research of Raz and Caine (1972) suggesting that α receptors played a predominant role in urethral contraction, though they had not identified which subtype of α receptors was related to the activity. (Yamanouchi 1994; Takenaka, et al. 1995) This led Takenaka and his

colleagues to conduct their own investigation of the distribution of the subtypes, as described in his statement above. Takenaka's connection with a urologist was the turning point of his work. He put it thus:

> An unexpected enquiry about whether our company was dealing in a classic α blocker came from a urologist friend of mine when we were doing the research. ... Because I couldn't understand why he was interested in such a drug, I went to ask him. Then, I found that he wanted to try the drug to improve his patients' urination because the Israeli [Raz and Caine's] research said it could do this. ... I answered him that I couldn't provide any immediately but that I would likely be able to provide the drug soon. Therefore, just at that time, the lead compound, the concept and the idea of its application came together. (Interview)

Secondly, the area of urology had not been well-developed as a market for the pharmaceutical industry. The competition was not considered to be fierce and a good business opportunity was expected there. Thirdly, Yamanouchi staff had established a connection with urologists through the development and marketing of an antibiotic for urinary tract infection. The area was a new and strategically important market for them. They were able to hear urologists' views and exchange information with them through their medical representatives. (Takenaka interview)

The research team found that the receptors that mediate contraction of the smooth muscle in the lower urinary tract and prostate gland of the rabbit are α_1 receptors. (Honda, Miyata-Osawa and Takenaka 1985; Takenaka, et al. 1995) Their subsequent study, in collaboration with urologists at the University of Tokyo, showed that the human urinary bladder base and prostatic urethra are also mediated by α_1 receptors. (Kunisawa, et al. 1985)[19] This opened the way to applying YM-12617 to the treatment of urination disorder accompanying BPH.

[19] The collaboration with the university was a key to the unprecedented research because animal experiments did not guarantee the same results in human beings and because the company could not do experiments with human tissues on its own, according to Takenaka (Interview).

7.4.4. Acquisition of the Internal Authorisation

Yamanouchi decided in 1982 to develop YM-12617 as a drug for the treatment of urination disorder accompanying BPH. There were several other similar candidate compounds, but YM-12617 was chosen because it was believed that its overall record in potency, pharmacokinetic properties and costs was best of all.

The acquisition of approval, from the company management, for the development of YM-12617 was the most crucial barrier facing the research team on the path to turning their discovery into an innovation.[20] The management was full of doubts about the marketability of the drug.[21] First, there was a doubt as to whether BPH could really be considered to be a disease. Secondly, this drug would reduce the necessity of surgery for the treatment of BPH.[22] There were questions about whether the drug would be accepted by practitioners and how it would coexist with surgery. There was also the problem of how high a price should be set to balance the anticipated decrease in doctors' income from surgery.[23] Thirdly, there was a problem of estimating the potential market size for this drug, because many patients of BPH at the time were unwilling to go to urogenital clinics.

The connection and communication with urologists played an essential role in sweeping away these concerns. Takenaka, the project leader, had an interest in medical needs and actively investigated this with the marketing staff. They found that a group of urologists at Gunma University had been doing studies on BPH for a long time in a village in Gunma Prefecture. This data provided Takenaka's team with a valuable basis for estimating the number of potential patients. Market information

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[20] This paragraph is based on the interview with Dr Takenaka.

[21] The procedure for decision making had already been institutionalised in Yamanouchi in the 1980s. First, a research group leader would propose the development of the drug to the assessment meeting inside R&D. Then, if the proposal were approved by the assessment meeting, it would be proposed in the management meeting. The decision of the management meeting would be final. (Takenaka interview)

[22] This is a common problem in the cases of histamine H_2 antagonists and of anti-prostate cancer drugs. See Chapter 5 and 6 of this thesis.

[23] A higher drug price implies a higher income for doctors in the conventional Japanese health care system. This is because of the margin between the official price and the amount actually paid to purchase the drug. See Section 5.4.2 of this thesis.

obtained from urologists like this enabled Takenaka to prepare evidence good enough to persuade the management. (Takenaka interview)

Economic reviews were conducted systematically by the company even after the approval for development had been given by the management. An expert department of the company assessed the project at least three times: before Phase I, before Phase III and before the application for governmental approval. They estimated the market size and sales, development and production investments and operational costs. It was their policy to proceed as fast as possible when the results were good. Therefore, the economic review had a significant influence on the speed of development. (Takenaka interview) Because the company had at first estimated the number of patients for the drug as being 50,000, the priority of the project was not very high until 1985. By an improvement in the technology used in the medical check-up of the disorder, the estimated number of the patients was corrected to being 150,000. After that, the priority of the project rose greatly. (Nihon Sougou Kenkyusyo 1998)

7.4.5. Technological Changes in the Development Process

In 1983, Yamanouchi started clinical trials of the drug, following its pre-clinical tests which had started in the previous year. (Nihon Sougou Kenkyusyo 1998) There was no practical problem in Phase I and Phase II. However, it was known that YM-12617 was a racemic mixture and that only its (-)-isomer was clinically active. An American consultant of Yamanouchi suggested to the company that the racemic property of the drug might become a significant problem in marketing in the United States and European countries.[24] The company knew that the single isomers of the drug would be at most twice as active as its racemic mixture and that it would cost a lot to produce the single isomers, together with the loss of time and money that they had already spent for the clinical trials of YM-12617. Nevertheless, the company decided "with tears" to switch the drug to the single (-)-isomers because they wanted to use the drug strategically as a decisive step for the company's globalisation. They

[24] There was also the same opinion in academia from the viewpoint of drug safety and Yamanouchi was aware of this. (Takenaka, et al. 1995, 778; Ariens 1984)

re-started the clinical trials of the (-)-isomers of YM-12617, now named tamsulosin, from Phase I in 1986. (Takenaka Interview)[25]

Another problem was the control of a minor side effect. Although tamsulosin was selective to the receptors at the prostate and the urethra, it also had a weak influence on blood pressure. This can cause orthostatic hypotension, dizziness felt on standing up. In order to avoid this disorder, the Takenaka group, at first, tried to increase gradually the dosage of the drug so that the body could get accustomed to it. This method was, however, very bothersome for doctors and patients. Therefore, they considered making a sustained release preparation of the drug to avoid the side effect. They succeeded in realizing this and achieving an oral, once-a-day administration in 1986. (Takenaka interview; Fukai 1995, p.489; Yamanouchi 1994; Takenaka, et al. 1995) This was also commercially important. Takenaka put it thus:

> We chose a sustained release preparation for the drug and this was another key factor in the success. This was done intentionally. We considered the business aspect very much at that stage. We had many talks with doctors and heard them say, "Sustained release is better," "Yes, this is good," and comments like that. (Interview)

Commercial consideration was also seen in Yamanouchi's efforts to establish an economical large-scale production system for the drug. They considered the abandonment of the other isomers, namely, (+)-isomers, to be a waste. They succeeded in the recycling of the isomers to turn them into (-)-isomers and reduced the production costs enough for them to be acceptable. (Takenaka interview)

7.4.6. Clinical Trials and Promotion

In the clinical trials of tamsulosin, the cooperative attitudes of doctors toward the trials were important. For example, doctors could use placebos in the clinical trials. But, it was, and it has probably been, extremely difficult for them to use placebos in clinical trials, under the practice of informed consent, in Japan. However, a

[25] The establishment of an economical, large-scale synthetic procedure was also reported to promote the switch. (Fukai 1995, p.489)

comparison with placebos is the most convincing way of showing the efficacy and safety of a drug. Yamanouchi succeeded in obtaining doctors' cooperation to use placebos in Phase II and Phase III of the clinical trials of the drug. They also succeeded in obtaining doctors' agreement to conduct more-detailed dosage response tests. Moreover, they persuaded doctors to apply the US guidelines, which were stricter than the Japanese counterparts, to the trials. With the cooperation of doctors, they achieved a high quality of clinical trials, which confirmed the efficacy and safety of the drug. (Takenaka interview; Kawabe, et al. 1990)[26]

The market was shaped partly by the company and partly by other actors in Japanese society. Takenaka put it thus in my interview with him:

> **Takenaka:** Social needs in the treatment of BPH changed and influenced [the development of the drug] positively. More men went to urogenital clinics. Doctors wrote about the urination disorder in newspapers, and people recognized it.
> **Hara:** As a disease?
> **Takenaka:** Yes, luckily. We promoted it intentionally to some extent, but there was a limit to what we could. After all, society did it. And the concept of QOL [quality of life] penetrated deeply in the society. You wake up frequently at night for urination, so you can't have a good sleep, and this is a bad quality of life. We need a drug to improve the situation. It was the time such thoughts emerged.

Scientific and technological progress also affected the progress of the development and sales of the drug. In 1987, subtypes of α_1 receptors were pharmacologically found and named α_{1A} receptors and α_{1B} receptors. (Morrow and Creese 1987; Minneman, Han and Abel 1988) Lepor, et al. (1993) showed that the α_1 receptors which mediate the contraction of the prostatic smooth muscle are the α_{1A} subtype. Later, by using molecular biology, three subtypes of α_1 receptors were found to exist, re-named α_{1a} receptors, α_{1b} receptors and α_{1c} receptors. (Schwinn, et al. 1990; Lomasney, et al. 1991) Price, et al. (1993), using techniques of molecular biology, identified that the α_1 receptors which predominantly exist in the prostate

[26] The size and the format of clinical trials of tamsulosin were praised by both editors of *the Journal of Urology*. (Wein 1990; Lepor 1990)

are the α_{1c} receptors (which encode for the pharmacological α_{1A} receptors).[27] Several studies showed that the affinity of tamsulosin to the pharmacological α_{1A} receptors and the cloned α_{1c} receptors is greater than that to the α_{1B} receptors. (Abrams, et al. 1995) These studies showed that tamsulosin is selective in the prostate because of its high affinity to the α_{1c} receptors (or, the pharmacological α_{1A} receptors). According to Takenaka, "this completed the scientific concept of the drug." (Interview) He described how this worked in the marketing of the drug:

> The influence [of the concept of the α_{1A} blocker] was enormous. In particular, when the word "selectivity" appeared, I could announce that I had discovered a selective drug. It was a scientific achievement. I could write many papers on it and become famous. This made the marketing of the drug very easy. "How is it different from existing drugs?" "Doctor, this is α_{1A} selective." "What's α_{1A}?" "Well, you don't know? α_{1A} is the one that is widespread in the prostate." "A-ha! So it works on BPH." Like that. We could give a very simple explanation. (Interview)

Tamsulosin was launched in Japan in August 1993 under the trade name of Harnal. As I already mentioned, it was also launched in the US and European countries later. The drug was exclusively developed by Yamanouchi. There were approaches from several companies about co-development but Yamanouchi declined them all. (Nihon Sougou Kenkyusyo 1998) The experience of the international development of the drug was a crucial step for the globalisation of the company[28]. (Interview) To my question of what was the most important factor in the success, Takenaka mentioned leadership and teamwork and emphasized the role of the experience of success in them. (Takenaka interview; Nihon Sougou Kenkyusyo 1998) He put it thus:

> While I had been researching receptors, I had also made several drugs from the research. Some of them succeeded commercially, others not. But when I researched something, I made a drug from the research and led it to the market. I did Pulsan, then I did Perdipine, and then Lowgan, and this Harnal.

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[27] The pharmacological classification of α_1 receptors and their molecular biological classification had not been consistent until recently. (Forray, et al. 1994; Kirby and Pool 1997)

[28] Yamanouchi has a bitter experience of the co-marketing of famotidine. See Section 5.4.

> Then Hypoca.[29] I materialized and commercialised research as drugs, so the management looked at me positively.
> ... After all, to be trusted is important. If you are trusted, you can do things as you like, to some extent. Then, you can take some risks. It's important to have experience of success. People who have experience of success can do something radical. (Interview)

7.5. Discussion

7.5.1. Types of Innovation

The innovation process of mevastatin clearly demonstrates the properties of the paradigmatic innovation discussed in the previous chapters. There had been no exemplary drug before mevastatin. It was this compound that played an exemplary role later. Although there had been a theory on the biosynthesis of cholesterol in the body before mevastatin, the compound demonstrated the idea of lowering the cholesterol level in the blood by inhibiting HMG-CoA reductase and showed what this kind of compound could achieve. Because of this novelty, scientific and technological uncertainty was very high. There was little knowledge about how to obtain the target compound. Endo bet on microbes. It was fortunate for him that a microbe did produce such a substance. Endo and Kuroda had to design an assay system to identify the substance. Even after the discovery of the substance, they had to discover how to demonstrate its efficacy in animals, because its initial tests with rats failed to show this. Organisational resistance based on unfamiliarity with the concept of the compound arose in the company Endo was working for. The project was almost axed again and again. Each time it happened, Endo had to take defensive actions. In particular, he mobilised academics including Goldstein and Yamamoto as a source of power. Without Endo's strong leadership, the project would have been axed. Although this compound itself was indeed abandoned after Endo's departure, its several analogues were developed by different companies and each of them achieved great success.

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[29] Pulsan®, Perdipine®, Lowgan® and Hypoca® are the trade names of indenolol, nicardipine, amosulalol and barnidipine, respectively.

In contrast, in the case of cefotiam, scientific and technological uncertainty was not so high as in that of mevastatin, because there were several exemplars, that is, the "first generation" cephalosporins. What the Takeda researchers had to do was to modify the molecular structure of the exemplars in order to obtain a significantly better one. However, existing patents, access to raw material and the room for improvement limited the opportunity for modification. Morita, the project leader, organised a number of researchers to achieve the task systematically, though he also added an element of competition to the process. The company made organisational efforts to make the drug competitive in various aspects: efficacy, range of target bacteria, safety, production costs, and convenient preparations. In each aspect, the construction of its differences from existing cephalosporins without harming its competitiveness was essential. Therefore, in the aspect of production costs, the covering of differences was the task, because from the beginning its production process was forced to be different due to the patents of other companies. Thus, the case of cefotiam clearly demonstrates the properties of modification-based innovation.

The case of tamsulosin was ambivalent. The compound itself was not so novel as in paradigmatic innovation, because α-blockers were well-known compounds. It had exemplars as compounds. Therefore, uncertainty in synthesis was not very high. However, the drug has novelty in its application, that is, the treatment for urination disorder accompanying BPH. Social uncertainty was high because people inside and outside the organisation were doubtful about the practicality of the idea of using an α-blocker as a drug for the treatment of urination disorder. Takenaka defended the project from this suspicion by providing evidence, including the potential market size of the drug, by himself. The company promoted the drug by using the concept of α_{1c}-blockage, which explains its selectivity in the prostate. In this process of shaping a new application, the linkage with doctors in the urological area was in particular important. They provided Takenaka and his company with the idea, the evidence and the concept. However, without the heterogeneous engineering conducted by Takenaka and his colleagues, the idea might not have succeeded. Thus, the case of tamsulosin has some properties of paradigmatic innovation and some properties of

modification-based innovation. This ambiguity can be attributed to its novelty in application and the familiarity with its molecular structure. Therefore, I propose to regard this as belonging to another type of innovation and name the type the application innovation.

7.5.2. Interpretative Flexibility and Organisational Authorisation

The cases in this chapter reveal how a pharmaceutical company is not a monolithic organisation. On the contrary, in the company there are divergences of opinions among researchers, between researchers and toxicologists, between researchers and marketing staff, and between researchers and the management. In the case of mevastatin, there was interpretative flexibility[30] about the efficacy and safety of mevastatin, with Endo and researchers at the Central Research Laboratories, and Endo and toxicologists at the company, having different views. The researchers on the Central Research Laboratories thought that the drug did not work because it did not lower the plasma cholesterol level in rats, whereas Endo thought that the drug failed to show its efficacy because the animal tests was not appropriate. The toxicologists believed that mevastatin was not safe enough because they observed unknown deposits in the liver cells of the rats given a large amount of the drug, whereas Endo believed that it was safe because the deposits were resoluble cholesterol ester. About the toxicity study that led to the suspension of the development of mevastatin, the company considered that mevastatin was not safe enough because the long-term tests demonstrated its potential toxicity, whereas Endo considered that mevastatin was safe because the tests had flaws in the choice of dosage. In the case of cefotiam, there was also interpretative flexibility about the safety of SCE-785, the prototype of the compound. Morita thought that the compound should be examined in humans because humans were not the same as the rabbits which showed its toxicity, whereas toxicologists thought that it should be abandoned because the activity of the drug in rabbits probably represented its activity in humans. In addition, there were other kinds of divergence of opinions in the cases in this chapter. In the case of cefotiam, there were doubts about the possibility of

[30] On interpretative flexibility, see Section 2.1.2. of this thesis.

further improvement of cephalosporins and about the profitability of the new cephalosporin among the people inside the company. In the case of tamsulosin, there were also doubts within the company about marketability and profitability.

It was the task of the project leader to obtain organisational authorisation despite the existence of these divergences and doubts within the company. Various resources were mobilised for this. In the case of mevastatin, the hens that were informally obtained from other laboratories and the linkage with an external medical academic played an important role in obtaining organisational authorisation. In the case of tamsulosin, the track record of the project leader, the linkage with external medical academics and doctors, and the social awareness of the quality of life were significant in the shaping of organisational authorisation. In the case of cefotiam, although the project team obtained organisational authorisation from the beginning, they had to demonstrate the feasibility and profitability of the compound in order to sweep away doubts within the company. In order to achieve this, their organisational capability was crucial. Thus, obtaining organisational authorisation was a very important aspect in any type of innovation, and various elements including social networks, non-human entities and organisational activities were mobilised for achieving this.

7.5.3. Culture, Social Structure and Innovation

The three cases of the Japanese pharmaceutical innovation described in this chapter show the influence of structural and cultural factors on the innovation process of pharmaceuticals. The case of mevastatin shows the importance of consensus in the Japanese organisation. The project-coordinating meeting played a decisive role, and the project could not go ahead without the agreement of toxicologists and pathologists. It also demonstrates the power of clinicians, particularly those at universities, in Japan. But for the offer of clinical trials from Yamamoto at Osaka University, the project of mevastatin would have been axed earlier. The case of cefotiam, the existence of a special society of clinicians, namely the Japan Society of Chemotherapy was highlighted. This well-organised society facilitated the

development of antibiotics in Japan. In the case of tamsulosin, the unwillingness of Japanese people to go to urogenital clinics and the difficulty of the practice of informed consent in Japan were indicated. Although the extent to which each of these cultural and structural factors affects the innovation process of pharmaceuticals seems to be varied, it is clear that these factors increase the complexity of innovation process in the pharmaceutical industry.

Chapter 8: Conclusion

In the previous chapters, we examined more than ten British and Japanese drug innovations in four different therapeutic areas: namely, cardiovascular diseases, bronchial asthma, peptic ulcer and prostate cancer. In addition, we also investigated three more cases of pharmaceutical innovation in Japan. The processes of these innovations may appear to be linear if we look only at their formal aspects. However, close examination of the processes reveals that this is not the case. They were not linear but much more complex. They included various properties: diversity, serendipity, interpretative flexibility, interactions between various human actors and between human and non-human actors, corporative strategy, leadership, heterogeneous engineering, organizational resistance, reverse salients, controversy, selection, regulation, market estimation, cost reduction, persuasion, promotion, rhetoric, politics, social acceptance, and so on. Scientific knowledge, technical knowledge, managerial knowledge, knowledge about organisation, economic knowledge, knowledge about clinical practice, knowledge about markets, knowledge about regulation and knowledge about society in general were newly combined or created in the process of transforming a chemical into a drug. At the same time, a lot of materials were constructed: compounds, assay systems, disease model animals, scientific equipment, production equipment, plants, packages, specialised inhalers, and so on. Various institutions were also established: project teams, project evaluation boards, clinical study groups, regulations, guidelines, and so on. Thus, the shaping process of a drug is a co-creation of materials, knowledge and institutions.

Although numerous lessons may be extracted from the cases this study includes, I highlight three major findings here: the shaping process of drugs, the different types of pharmaceutical innovation and the features of Japanese pharmaceutical innovation. In the rest of this concluding chapter, I will first describe the shaping process of prescribed drugs in a more specific way than the description above but in a more general way than in each case study. I will then propose three different types of drug innovation, which emerged from the case studies. Each of the types has different profiles in its shaping process. Next, I will examine differences between the UK and

Japan in pharmaceutical innovation. Finally, I will discuss some theoretical and practical implications of this study.

8.1. The Shaping Process of a Drug[1]

A prescribed drug is shaped by various factors, as mentioned above. Although the shaping process is complex, it is not chaotic. This is because shaping technology is an activity in which people pursue certainty in an uncertain world. (Munakata 1989) This purpose cannot be completely achieved, but gives the shaping process of technology some distinguishable profiles. We can distinguish four aspects of the shaping process of a drug. Each aspect can be characterised and distinguished by the main activities and the main actors it includes. The aspects of the shaping process of a drug consist of the shaping of the compound, the shaping of the application, the shaping of organisational authorisation and the shaping of the market. In this section, we will see what kinds of activity and actor play what kinds of role in each aspect of the shaping process of a drug. At the same time, we will examine how the objects of the process, the compound, the application, organisational authorisation and the market, are shaped.

8.1.1. The Shaping of the Compound

The first aspect of the shaping process of a drug is the shaping of the compound. The compound here refers to the material aspect of a drug. The core of the compound is a chemical believed to have a profile of biological activities of clinical use. Therefore, this aspect includes the process of drug discovery and biological and clinical tests. However, the compound here also includes later modification of the molecular structure, preparation (formulation) for its practical use and any other materials used for its practical use. Several actors and factors play a significant role in this aspect. Let us examine them one by one.

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[1] As discussed in Section 2.1.4, I use the words "the shaping of technology" rather than "the social shaping of technology" in order to withdraw the *a priori* priority of the social.

First, in the shaping of the compound, the primary player is the leader of the research project, whose interest and expertise orients the direction of and limits the range of the search for the compound. James Black's interest and expertise in beta-blocker and H_2 antagonists, David Jack's in anti-asthma drugs, Masahiko Fujino's and Barry Furr's in LHRH analogues, Akira Endo's in HMG-CoA reductase inhibitors, Toichi Takenaka's in receptor-based drugs, and Katsura Morita's in cephalosporins were the driving forces of their research projects, which eventually led to the discovery of drugs.

Second, the knowledge and skills of the research team and the company also limit the area of research. As we saw in Chapter 2, drug discovery means the discovery of the "fact" that a chemical has a biological activity that can be clinically useful. Therefore, cooperation between chemists and biologists is essential. Their different expertise may also guide the research in a specific direction. Glaxo's intellectual assets in steroids, Takeda's and ICI's in peptide synthesis, Sankyo's fermentation, Yamanouchi's in adrenergic receptor-based drugs and Takeda's in antibiotics, embodied in fellow researchers and supporting staff, probably facilitated research in specific areas. However, the shaping activity of a compound also contributed to the accumulation of these intellectual assets. It was seen in the pairs of innovation in the same organization, such as propranolol and atenolol, salbutamol and salmeterol, BDP and fluticasone propionate, and mevastatin and pravastatin. Thus, the intellectual capability of the organisation in biology, chemistry and relevant scientific disciplines is an important factor.

Third, the material conditions of the research team and the company constrain the research. This is closely related to the intellectual assets described above. Intellectual assets are always accompanied by specific non-human entities: for example, assay systems, model animals and special experiment equipment. These entities also seem to make some research areas easy but others hard to accomplish. For example, Glaxo had patented steroids when Jack looked for anti-inflammatory substances, and that probably significantly affected his choice and eventually resulted in the development of inhaled steroids. In contrast, mice used in tests may have prevented mevastatin

and its analogues from becoming a drug, because it showed the ineffectiveness of the series of drugs in lowering the level of cholesterol. In addition to Endo's obsession with the substance, however, hens, then dogs and monkeys, helped Endo to overturn the previous belief about mevastatin's ineffectiveness. Of course, strictly speaking, these animals did not intend to prove or disprove the belief and it was people who believed or disbelieved the proof, [2] but without them mevastatin and its analogues may have been discarded in practice.

Fourth, linkage with the frontiers of relevant science and technology outside the organization is also important. Researchers can obtain new knowledge or improve their existing expertise from an external network. In particular, in Japanese cases such as the discoveries of leuprorelin and mevastatin, links with state-of-the-art science in the US played a crucial role: providing the leading researchers with specific research interests. In contrast, in British cases, their intellectual sources seemed to be more domestic. Some key researchers including Black and Furr had worked as academic researchers before they joined pharmaceutical companies. The range of the external network, however, is relatively narrower in this aspect than in others: normally, it does not include clinicians and engineers. Special science and technology disciplines seemed to be particularly influential. Knowledge transfers were normally conducted through literature probably because researchers possessed the relevant tacit knowledge and understood and speculated about others' work. However, when a research organisation does not possess the relevant tacit knowledge, sending people to or collaborating with other organisations having the knowledge is necessary. (Collins 1992, pp.51-78) This is observed in the case of nicardipine in which researchers were sent to universities to learn necessary techniques for experiments and in the case of leuprorelin in which the research team was in collaboration with another company in order to develop the biodegradable polymer for its depot preparation.

Fifth, the strategy of the company sometimes affects the properties of the compound. In the case of cefotiam, Takeda's strategy to enter the cephalosporin market was the

[2] Relevant discussion here is found in MacKenzie (1996a, pp.13-16) and Collins and Yearley (1992).

starting point of research. In the case of ranitidine and famotidine, Glaxo and Yamanouchi were looking for anti-peptic ulcer drugs when Black discovered H_2-antagonists. Their previous strategic choice of the therapeutic area probably encouraged the Glaxo and Yamanouchi researchers to conduct their own research on H_2-antagonists. In the case of tamsulosin, Yamanouchi strategically wanted the drug to be internationally competitive. Regulatory bodies, in particular those of American and European countries, preferred purer compounds as drugs. Therefore, they chose to switch from the racemic mixture of the drug to the single isomers that were effective, even though they had to spend a lot of money and time over the change.

Sixth, market needs also sometimes affect the properties of the compound. Here, the notion of reverse salients (Hughes 1983, pp.79-105) seems to be useful. The search for anti-cholesterol drugs resulting in the discovery of mevastatin was driven by Endo's recognition of potential market needs. In the case of anti-asthmatic drugs in Glaxo, two approaches, bronchial dilation and anti-inflammation, were adopted for the treatment of bronchial asthma. When bronchial dilation was achieved by salbutamol, anti-inflammation became the reverse salient. When it was solved by BDP, the short duration of action of salbutamol became the reverse salient because other companies launched longer acting bronchodilators. Then, salmeterol eliminated the reverse salient. Fluticasone propionate resolved the reverse salient of BDP, namely moderate potency. It is important to notice that these reverse salients emerged not only when relevant technologies or therapies advanced but also when rival companies launched competing products. This role of competition should be added to the discussion of reverse salients. Perceived potential demand also explains why LHRH analogues such as leuprorelin and goserelin appeared on the market as their depot preparation. The inconvenience of daily injection urged the Takeda and ICI researchers to develop more convenient forms of the drugs. A similar example is also seen in the case of the development of preparation of cefotiam.

Seventh, the regulatory systems significantly affect the properties of the compound, though their influence is not always clearly observed. However, it is obvious that the level of acceptable toxicity and efficacy of the compound are defined by the

regulation. The quality and purity of the compound are also controlled by the regulation. For example, tamsulosin was switched late on in its R&D process from being a racemic mixture to being the single isomer. This was because the regulators, especially American and European ones, preferred purer compounds. In the case of leuprorelin, it was in practice impossible for Takeda to sell the drug for daily injection because the Japanese regulator did not permit self-injection. This encouraged the development of the depot preparation of the drug.

Eighth, competitors have an influence on the shaping of the compound. Their patents limit the range of possible compounds. When researchers at Glaxo or Yamanouchi tried to modify the molecular structure of an existing compound in order to discover a new H_2 antagonist, they had to avoid infringing patents of SmithKline & French. This led them to the somewhat unique molecular structures of ranitidine and famotidine. LHRH analogues and their preparations were different because the latecomers had to avoid existing patents of rivals. On the other hand, competitors also have a positive influence. Their patents and other publications may help the search for a new drug. The work of researchers at SmithKline & French Laboratories gave a concept of H_2-antagonist to researchers at other companies including Glaxo and Yamanouchi. A similar intellectual spill-over between rivals was also seen in the case of LHRH analogues.

Ninth, serendipity sometimes plays an important role. For example, cardio-selective β-blockers, the paradoxical effect of LHRH analogues, two phases of release of goserelin depot preparation and the cyclisation of the side chain of cephalosporins were all serendipitously discovered. This implies the role of non-human entities in the shaping of the compound. Although serendipity includes cognitive and social activities as well, without the independent activities of non-human entities it would not have happened. The shaping of the compound is a complex process in which not only human actors but also non-human entities play an active role.

Tenth, production costs may also affect the choice of the compound. As is suggested in the case of leuprorelin, production costs seem to be taken into consideration in the

choice of the compound, when there is more than one compound with similar properties.

8.1.2. The Shaping of the Application

The second aspect of the shaping process of a drug is the shaping of the application. This is, in other words, the shaping process of the meanings of the compound in practice. The compound often has various biological activities. The same hormone or neurotransmitter often plays various roles in the body because their receptors at different places cause different reactions. For example, β adrenergic receptors not only dilate bronchi but also increase heart rate when they are stimulated by adrenaline. This is also the case in drugs mimicking the activity of naturally occurring hormones and neurotransmitters. That is to say, the compound often has plural potential activities.

The first two factors that limit the application of a compound stem from properties of the compound itself, in other words what the compound can do, and therapeutic needs, that is, what people need. This is why an H_1-antagonist cannot become an anti-peptic ulcer drug though it is used for the treatment of hay fever. This is also why β_2-blockers, which are of little clinical use, have not appeared on the market. Normally, these two factors, the range of activities of the compound and the range of therapeutic needs, narrow down the application of the compound to only one or one main and a few relevant applications. In some cases, however, more than one potential application may exist.

When these plural potential applications are unrelated to each other and one of them is clinically used, the others may cause side effects. For example, isoprenaline dilates the bronchi but at the same time increases the heart rate, which is dangerous for patients with heart failure. In such cases, the ambiguity of the compound is normally what should be eliminated. This should be done in the shaping of the compound. Drugs with selectivity such as β_2-stimulants and β_1-blockers were results of ambiguity reduction. However, when side effects of this sort are of little harm and

can be controlled, the ambiguity may be retained and the application of the compound is selected for various reasons. Such cases are not common, but tamsulosin is one. LHRH analogues are another example. In these cases, we can explore the shaping process of the application.

The third factor related to the shaping of the application, which was seen in the cases of LHRH analogues, is the cognitive ability of the project leader and other researchers to explore the potential applications of the compound. Researchers working on LHRH analogues at first thought that the main application of the drugs was fertility promotion. However, when they came across the "paradoxical effect" of LHRH analogues, the researchers turned their attention to sex hormone dependent diseases such as breast cancer and prostate cancer. This was possible because they had broad knowledge about potential therapeutic areas. They had planned the development of both agonists and antagonists of LHRH early on and had accumulated relevant knowledge about the potential therapeutic areas before their encounter with the paradoxical effect. Thus, the broad knowledge of researchers in therapeutic areas is an important factor in the shaping of the application. In other words, the intellectual capability of organisation across a range of therapeutic areas conditions the search for applications.

The fourth factor is an external network; in particular amongst clinicians from whom the researchers collect information about how to use the drug. In the case of tamsulosin, the key researcher heard of the possible new application of α blockers from a urologist. Without the linkage between the drug researcher and the clinician, such information would not have been transferred to the drug researcher and tamsulosin might not have appeared as a drug for the treatment of the urination disorder. Therefore, network linking to clinicians, who play an equivalent role to the "lead users" (von Hippel 1988), is important for the shaping of the application. The fifth factor is the competitor. As with the shaping of the compound, the behaviour of competitors has a spill-over effect. In the case of LHRH analogues, their makers entered the same therapeutic areas one after another.

The sixth factor is the size of the potential market of the drug. In the case of tamsulosin, if its market for urination disorder had been regarded as being much smaller than its hypertension market, Yamanouchi would have chosen the application for anti-hypertension rather than for the treatment of urination disorder. In the cases of LHRH analogues, Takeda, Abbott and ICI recognised that the prostate cancer area would be a more promising market for their drugs than other areas such as contraception and the treatment of gynaecological disorders because they thought that there was no stronger competitor in the former area. It should be noticed that the potential market is not just what exists but what is recognised as being able to be shaped. The recognition of the potential market probably overlaps with the shaping of the real market. In other words, the recognition of the potential market is a mental simulation of the shaping of the real market. Researchers' speculation about how much they will be able to expand the market is reflected in their recognition of the size of the potential market, which in turn affects the shaping of the application. The shaping of the real market will be discussed below.

8.1.3. The Shaping of Organisational Authorisation

The shaping of organisational authorisation means the persuasion of people inside the company, in particular the management. In the cases in this study, we can see that even people in the same organisation may resist to the development of a new drug when the concept of the drug is novel and unfamiliar to them. The background of this is the conflict between groups within a company over its limited resources. The clinical development of a drug costs a huge amount, as described in Chapter 2, and its failure seriously damages the financial situation of the company. The shaping of organisational authorisation can be regarded as the "micro" political aspect of the drug. In fact, in many cases, including nicardipine, salmeterol, burimamide, leuprorelin, mevastatin, tamsulosin and cefotiam, organisational resistance or criticism was observed. It was necessary for the researchers to obtain organisational authorisation. Without it they could not have realised the development of their drugs. Several factors play an important role in the shaping of organisational authorisation.

The primary player is the project leader. Endo had to gather evidence for the efficacy of mevastatin by himself after other researchers who had conducted the preliminary animal tests had denied it. He also had to arrange its clinical trials to reverse the decision of the company to abandon the development of the drug. Takenaka also had to provide the management with evidence for the marketability and profitability of tamsulosin. It was reported that researchers at SmithKline and French Laboratories in England also had to make a lot of effort to prevent the American parent company from cutting the project off. To convince people within the company, not only evidence but also the track record of the project leader was important. Black had such a reputation. Takenaka in the case of tamsulosin was trusted by the management because he had had several successful achievements in the past including the R&D of nicardipine. The position and power of the project leader in the company are also important. Jack in the case of salmeterol was the director of research and development at Glaxo at that time, and he could tell people to work on the drug instead of persuading them persistently. In the cases of leuprorelin and cefotiam, the project leaders succeeded in obtaining the support of the top management of the company.

The management is the counter player. The decision of "go or no-go" by the management (Kuwashima 1998; Pisano 1997, p.97) is the ultimate element in shaping organizational authorization. Unless they recognise the significance of the project, the discovery of a drug will not lead to an innovation. In the case of leuprorelin, Shinbei Konishi, the then president of Takeda, and Kunio Takeda, the then vice president of TAP Pharmaceuticals and a member of the Takeda family, supported the development of the drug in Japan and the US. Also, in the case of cefotiam, the then top management of Takeda backed the project in a somewhat top-down manner. In the case of nicardipine, Masuo Murakami, the then director of the central laboratory of Yamanouchi and a powerful figure in the company, gave Takenaka his approval. Jack, the head of research and development at Glaxo, himself actively led the projects of the anti-asthma drugs.

Thirdly, evidence for the future of a drug, such as the properties of the compound, estimation of marketability and profitability, and the distinguishable concept of the drug, is important. In other words, it is significant how well the compound and its application are depicted as a future drug. The drug's properties, which relate to efficacy and safety, are particularly important. If they are not good, the drug may have to be discarded in the development process or may be rejected by regulatory bodies. Even if successfully launched, it may have to be withdrawn or may earn little income. Estimation of marketability and profitability is a simulation of the shaping of the market. The potential size of market, the expected situation of competition and the estimated price of the drug are important in the decision making. In many cases, however, it was indicated that the forecasting of these parameters was extremely difficult in practice. This is understandable when we consider that uncertainty is very high in the pharmaceutical industry and it takes several years from the decision to the market launch. Therefore, these parameters are perhaps important but unlikely to be decisive. Rather, the concepts of drugs like "H_2," "α_1 selective" and "third generation" may be more convincing than the uncertain estimation of sales and profits. However, if the R&D assessment system is strictly institutionalised as is seen in the case of tamsulosin, the estimation of sales and profits is more critical and conditions the behaviours of proponents, opponents and decision makers. Internal workers involved in the estimation of market are likely to gain more power in this case.

Fourthly, linkage with external experts, in particular clinicians, sometimes plays an important role in supplying evidence. In the case of mevastatin, Endo used his network amongst worldwide researchers including Goldstein and Brown and domestic clinicians including Akira Yamamoto at Osaka University Hospital in order to enhance the credibility of his argument. Yamamoto's active proposal for clinical trials of the drug overturned the previous trends of opinion within the company. Takenaka and his colleagues used the data they obtained from clinicians at universities in order to prepare convincing evidence of the marketability and profitability of tamsulosin.

Fifth, corporate strategy affects the decision of go or no-go. Glaxo had a strategic interest in the anti-asthma area because of its potential size of market. Both Glaxo and Yamanouchi regarded anti-peptic ulcer area as strategically important. Takeda aimed at the establishment of its domain in the cephalosporin antibiotics area. Strategy thus promoted the projects of anti-asthma drugs and ranitidine in Glaxo, famotidine in Yamanouchi and cefotiam in Takeda. If the companies had had a strategy focusing on other therapeutic areas, the progress of the projects might have been delayed. In fact, in the cases of leuprorelin and goserelin, it was said that the projects were not given very high priority at first, though it is uncertain how much this affected the lead time from their discovery to market launch.

Sixth, organisational capability in recognising the value of new drugs is also important. Researchers of other groups and people belonging to divisions of clinical development, finance, production, marketing and sales may become opponents of the project. Their understanding of the concept of the new drug and their insights into pharmaceutical business significantly affect to what extent the project will face organisational resistance. The newer the concept of the drug is, the more difficulty people other than its researchers have in understanding it. The organisational resistance in the case of cimetidine seemed to be much more than that in the case of ranitidine or famotidine.

Seventh, changes in social values seem to have an influence on the decision making. For example, the rise in awareness of the quality of life in Japanese society possibly affected the approval of tamsulosin by the Yamanouchi management. The recent emergence of "lifestyle drugs," which improve the quality of life and alleviate the physical disorders of old age, including Viagra®, Prozac®, and HMG-CoA reductase inhibitors ("Losing the drugs war," *Financial Times*, April 13 1999) may reflect the similar worldwide change in social values. This change is now more obvious than before, and the projects working on this kind of drug find it easier to obtain organisational authorisation today. It is said that pharmaceutical companies are particularly sensitive to negative public response. (Clarke and Montini 1993, 54) It is possible that they will abandon their research in a particular area if the general

public criticises it, as was seen in the case of genetic modified crops. ("Monsanto drops GM 'terminator'," *The Guardian*, 5 October 1999)

8.1.4. The Shaping of the Market

The fourth and final aspect of the shaping process of a drug is the shaping of the market. This includes clinical trials, approval of regulatory bodies and marketing. More heterogeneous actors, particularly outside the company, are involved in this aspect than in others. This can be regarded as the "macro" social aspect of the drug. It is this aspect that is most closely investigated by other sociological works on drug development. (See Chapter 2.) In this section, we will examine what kinds of actor are generally involved in the shaping process of the market of a drug, though there are probably more relevant actors in specific cases. (E.g. Clarke and Montini 1993)

The first actor is the company, which defines the target market of the drug and tries to seize it. The definition of the target market has been mainly conducted in the shaping of the application and in the shaping of organisational authorisation. However, the company can redefine it in the process of shaping markets, including clinical trials and marketing. The ability of the company to identify the potential market restricts the range of their real market. This is a strategic as well as a cognitive issue. They have to decide their therapeutic and geographic domains. They also have to forecast the future of their business conditions and their own position. Their organisational capability also limits their future market. Unless they can secure sufficient money, production capability, cooperation of clinicians and patients, necessary sales force, expertise in legal and regulatory affairs, and management ability to organise these heterogeneous functions, the shaping of the market is unlikely to be achieved. Glaxo in the case of ranitidine most remarkably demonstrated their organisational capability to achieve the quick shaping of its worldwide market. Process development capability (Pisano 1997) is one of the key factors.

The second actor is the regulator, which officially approves the manufacturing and marketing of the drug within its jurisdiction. This is, in other words, the social authorization of the drug, and an analogue of the organizational authorization of the drug seen in the company. Of course, the values and criteria are probably different between the two. The safety, quality, efficacy and cost-effectiveness ("Clinical watchdog rejects anti-flu drug for NHS," *Financial Times*, October 1 1999) of the drug should be more important for the regulator than marketability and profitability, which is essential for the company. However, in practice, the difference is probably much less than it appears, because without the regulatory approval the drug cannot be marketed, and the value and criteria of the regulators are likely to be reflected in the management decision of the company. It is obvious that there is no market if the regulator does not approve the drug. As was seen in the case of pronethalol in Chapter 3, the prescribing restriction of the drug ruled by the regulator seriously limits the size of its market. As we saw in the case of practolol in the same chapter, the regulator may limit the market of a drug later on. In addition, the regulator in Japan determines the price of the drug, as mentioned in the case of leuprorelin and famotidine. This also affects the size of the market in terms of value.

The third actor is the doctor, who conducts clinical trials and prescribes the drug after its launch. Doctors directly constitute the drug market. Therefore, their evaluation of the drug is crucial for the establishment and expansion of its market. The leading clinicians in the therapeutic area of the drug play a particularly important role. Their support and collaboration are essential in the clinical trials. They often have interests in clinical trials and in the publication of results. The collaboration between the company and the doctors often results in the high quality of clinical trials, which in turn enhances the value of the drug amongst doctors and government officials. The opinions of leading clinicians on the drug also affect its valuation. In particular, in the highly hierarchical medical society in Japan (Campbell and Ikegami 1998, p.67), leading clinicians at universities have a very strong influence over the other doctors. This was typically observed in the case of procaterol.

Two activities are especially important to involve doctors in the shaping of the market of drugs: clinical trials and promotion. Clinical trials are very important to secure support from both doctors and regulators. They are the core evidence of efficacy and safety, and have a crucial influence on the evaluation of the drug. Leading clinicians learn the properties of the drug while they conduct its clinical trials. They in turn transfer their evaluation to practitioners, regulators and other people who are concerned with the drug. Thus, clinical trials are not only scientific experiments but also the process of shaping the market. However, as many scholars indicate (Marks 1997; Abraham 1995; Epstein 1996; Richards 1988; Bodewitz, Buurma and de Vries 1987), the results of clinical trials are not free from controversy, which affects the market of the drug. The occurrence of such controversy was observed in the cases of β stimulants and LHRH analogues. The settlement of these controversies was not achieved by "crucial" clinical trials but resolved by the redefinition of the problem or the accumulation of experience (both tests and uses) among medical society over a considerable time. Major players in such controversies are also clinicians.

After the launch of the drug, doctors who prescribe the drug, in other words, who can make their patients use it, directly constitute its market. As long as the cost of the drug is reimbursed by medical insurance systems, therapeutic properties of the drug rather than its cost normally affect their choice. New drug concepts such as "β stimulants," "Ca antagonists," "H2 antagonists," "super-agonist," "HMG-CoA reductase inhibitors" and "α_{1c} blockers" attract doctors' interests. Drug properties labelled as "new generation," "more selective," "longer acting," "safer" and so on also appeal to them. The latter was seen in the cases of latecomer drugs such as procaterol, ranitidine, famotidine and cefotiam. Ease of use can also become a good reason for choice. Depot preparations of LHRH analogues demonstrate this. Therefore, the shaping of the compound and its application strongly affects the shaping of the market. At the same time, however, it is also important for the company to inform and convince doctors that the drug has these advantageous characteristics. The means of promotion normally consist of clinical trials, academic papers, symposia, conferences, advertisements and visits by medical representatives.

Promotion based on scientific evidence is particularly important in this industry. In addition, the financial opportunity for doctors is important. If doctors suffer a significant decrease of income because of the substitution of the drug for the existing treatment, the drug is unlikely to be accepted by them. This can be seen in the cases of tamsulosin and LHRH analogues.

The fourth actor is academics who create knowledge, skills and artefacts related to the drug research and development. They are supporting the properties and concepts of the drug and results of clinical trials, which is the evidence of usefulness of the drug and the basis of marketability and profitability. They may, therefore, construct and destroy the market of the drug at any time. For example, a new technique using biotechnology identified subtypes of α_1 receptors, which explained the mode of action of tamsulosin and promoted its marketing. In contrast, as in a case study provided by Richards (1988), "randomised, controlled, double-blinded" clinical trials at the Mayo Clinic destroyed the market of vitamin C as an anti-cancer drug.

The fifth actor is the rival company having a competitive product in the same therapeutic area. There are both advantageous and disadvantageous effects in the shaping of the market. The advantageous effect was seen in the cases of LHRH analogues and nicardipine. The simultaneous clinical development of the same type of drug by different companies facilitated learning of doctors and regulators about the drugs. The disadvantageous effect is more obvious. Patients are limited in number, so companies must divide the market. Competition also affects the price of the drug, though its effect on the price seems to be complicated because of the regulation.

The sixth to eighth actors are patients, their families and carers, and activists. The number of patients who give their informed consent to clinical trials is essential for the company to develop the drug. This factor seems to explain partially the delay of the development of leuprorelin in Japan. In the case of drugs for the treatment of diseases that are not very serious, it is essential for the company to make patients aware of the diseases. In the tamsulosin case, it was necessary to make the BPH

patients visit clinics. Articles and lectures by opinion leaders, the advice of family doctors and advertisements by the company contributed to making the patients aware of the disorder and conveyed the idea that the disorder could be and should be cured by going to hospital. Patients, together with their families, carers and activists, may actively request the development and marketing of particular drugs, as was seen in the case studies of anti-AIDS agents and thalidomide. (Epstein 1996; Timmermans and Leiter 2000; see also Clarke and Montini 1993)

The ninth actor is the compound. The compound was defined as the chemical believed to have biological activities of clinical use. (See Sections 8.1.1. and 2.2.3.) Without the compound, of course, there is no market for the drug. However, because this is based on belief, the properties of the compound are not absolutely stable. It is possible that the efficacy and safety of the compound described earlier may become problematic in the process of clinical trials and practical uses. For example, safety of practolol became doubtful when the reports about its side effects appeared. The drug lost the market. When the safety of mevastatin became problematic, the company gave up its development rather than tried to re-establish the belief of its safety. Thus, mevastatin failed in the shaping of the market.

8.1.5. Interaction between the Different Aspects of the Shaping

I described four aspects of the shaping of a drug above. In each aspect, various actors, factors and activities are involved. Real shaping processes of drugs are probably much more complex and different from case to case. Although my description of the shaping process of drugs is not exhaustive, we can learn several important things from the examination of the factors discussed in this thesis.

First, several actors and factors are involved in each aspect of the shaping of a drug. Some intend to participate in the shaping process of the drug, whereas others participate without intention or awareness. Different actors sometimes give different meanings to the same drug. For example, for Endo, the project leader, mevastatin was a safe drug with a remarkable anti-cholesterol activity while for toxicologists at

Sankyo it was a drug with high uncertainty in regards to safety, and for some researchers at the Central Research Laboratories, it was something invented out of their labs. (See Section 7.2) As proponents of the SCOT (see Section 2.1.2) argue, such interpretative flexibility results in a diversity of candidate drugs (RWX-163, for example, in the mevastatin case); the closure mechanism is indeed a social, political process (networking among external specialists in the case). Second, however, not just human actors but also non-human entities play a role in each aspect, as advocates of ANT (see Section 2.1.3) insist. Actors are not naked. (Strum and Latour 1987 [1999]) Without non-human entities, human actors cannot shape drugs though non-humans alone, of course, cannot shape them, either: hence they constitute "heterogeneous" networks. Various material entities, including compounds (see Section 4.7.3), animals (e.g. mice and hens in the development of mevastatin), human bodies (e.g. the unexpected side effect of practrol), scientific instruments (e.g. ultrathin endoscopes in the case of famotidine) and production equipments (e.g. mixers in the case of leuprorelin depot) restrict or facilitate the shaping process. Although they never determine the process by themselves, their influences are indispensable. This may be described as the material imperative. Third, actors are not isolated from each other or from the wider context, including other actors not mentioned here. Actors interact with each other in the process of drug shaping. This interactive relationship between various actors in innovation process is consistent with the key argument of the social shaping of technology. (MacKenzie and Wajcman 1999, 3-27; Williams and Edge 1996, 867) Many actors observed in case studies here are those that were mentioned in other sociological studies in the biomedical and pharmaceutical area. (See Section 2.2.4.3) Fourth, relevant actors seem to become more external, more heterogeneous and more institutional in the shaping of the market than in the shaping of organisational authorisation, in the shaping of organisational authorisation than in the shaping of the application, and in the shaping of the application than in the shaping of the compound. This appears to be consistent with the argument of technology studies that technology is more heterogeneous and a more diverse range of institutions than science. (See Section 2.1.5.) However, this does not mean that external and institutional factors have no influence on the aspects of the shaping of the compound and of the application.

Rather, their influence seems to be more indirect and more likely to be mediated by the researchers' cognition in these aspects than in the shaping of the market.

Fifth, the most important finding here is that the four aspects of shaping of a drug interact with each other. The compound limits the shaping of the application. The compound and its proposed application are key factors for the project leader to persuade management. Therefore, they limit the shaping of organisational authorisation. They are also key factors for the company to apply for approval of the regulator and to promote the drug amongst doctors. So, they also limit the shaping of the market. The shaping of the application can be regarded as the cognitive simulation of the shaping of the real market. As was seen in the case of tamsulosin (Section 7. 4), unless the potentially profitable application is recognised by pharmaceutical companies, the market of drugs will not be exploited. The organisational authorisation of the compound conditions the shaping of its market. Without organisational authorisation, it is obvious that the compound cannot become a drug, as we can see in the case of mevastatin.

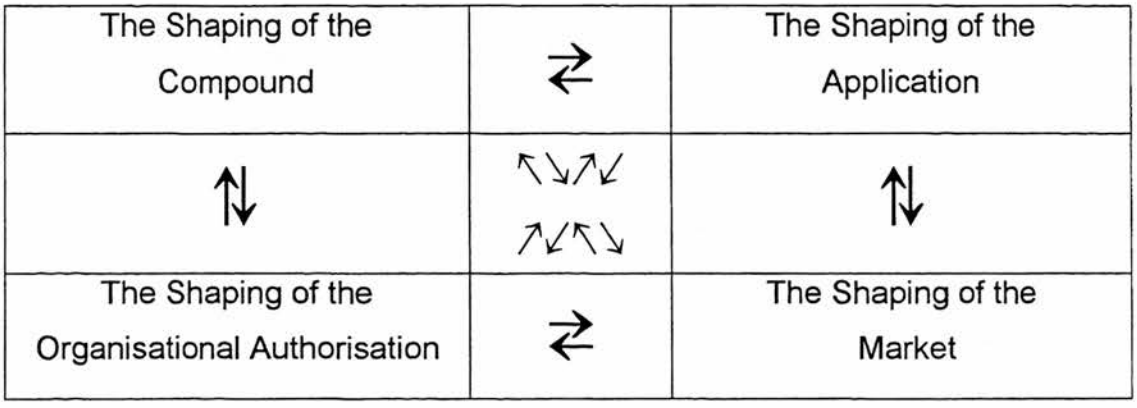
There are also influences in the opposite direction. The application sometimes affects the shaping of compound. For example, in their use for the treatment of prostate cancer, LHRH analogues should be given to patients every day to obtain the paradoxical effect. For this, depot preparation had to be developed. Organisational authorisation, in which the marketability and profitability of the drug are discussed, limits the choice of the compound and its application by researchers. It is unlikely that they will choose a drug or an application which seems to be unmarketable and unprofitable. Yamanouchi, for example, gave up the development of their latest calcium antagonist, because they doubted its competitiveness and profitability, given the relatively low prices of anti-hypertension drugs. (See Section 3.4) The market also affects all aspects of the shaping of a drug. The market restricts the decision of management as to whether they authorise the development of the drug. If the possibility of the successful shaping of the market seems to be slim, the project of the drug will probably fail to obtain approval by management. The needs of the market, therefore, have an influence on the shaping of the compound and its application.

Market needs basically restrict the range of the search for applications. Two things, however, should be noticed: first, the market is not clear at all in advance; second, the market is not what exists in advance but what is constructed. This can be said of most cases in this study. Therefore, on the one hand, the cognitive abilities, insights and visions of research leaders and management mediate the influences from the market to the shaping of the compound, the application and the organisational authorisation. On the other hand, the practical ability of the company to achieve the shaping of the market also modifies these influences, though other contingent factors such as regulation, medical sciences and social movement also intervene in the real shaping process of the market. The constructed nature of market is in accordance with the discussion by SST authors. (Williams and Edge 1996, 877)

Thus, the four aspects of the shaping process of a drug are interactive. They are not sequential but overlapping and co-evolving. The interactive relationships include not only explicit and observable ones but also implicit and cognitive ones. Because human actors speculate about the results of their activities, speculated results sometimes play a role in the shaping process. This anticipative behaviour of actors involved in innovation process such as scientists and companies are consistent with the arguments of Webster (1991, pp.48-50, p.59) and McKelvey (1996, p.226). Market constituencies including doctors, patients and regulators are also likely to accept drugs they believe to be scientifically reasonable and technologically reliable in terms of efficacy and safety. Therefore, it can be said that each of the four aspects is reflected in all the others through the anticipative ability of relevant human actors. The four aspects are also inter-dependent. If one aspect becomes unstable, all the others also become unstable. For example, if the safety of the compound becomes problematic, its application, its organisational authorisation and its market also become questionable. If the market of a class of drugs dwindles, a new compound of the class for the conventional application is unlikely to appear. Even if it happened to appear, the management would probably axe the project. In sum, a drug emerges only when all its four aspects are successfully shaped and being shaped. The compound, the application, the organisational authorisation and the market

collectively support drug innovation. Figure 8.1 schematises the interactive relationships between the four aspects.

Figure 8.1: Interactions between the Four Aspects of Drug Shaping



It should be noted that the inter-reflection is neither perfect nor exclusive. There are always contingencies and actual results of any action are not exactly the same as anticipated ones. They are inter-dependent but not self-contained. It is possible for us to regard them as a network consisting of various actors, factors and activities including: the project leader, various specialists, material resources of the organisation, external network linking industrial researchers with academic scientists and clinicians, the management, the cooperative strategy, the organisational capability, market needs, market size, regulators, doctors, competitors, patients, families and carers, activists, journals, conferences, protocols, dossiers for approval, concepts of drugs, and so on. New factors can enter the network at any time and transform or even dissolve it. Relevant non-human entities may change the network without intention. Humans can intentionally transform or scrap the network. Humans also alter the network without or against their intention. Thus, the shaping process of a drug is a networking activity, which is like the one that actor-network theorists describe. (See Section 2.1.3.) It includes both the "social" and the "material." It can be altered. This transformation of the networks surrounding drug development processes also seems to share a lot of points with the discussion of dynamic networking related to vaccine development by Galambos and Sewell (1995).

Finally, it should be noted that the products of the shaping process of a drug are not only the drug but also various sub-products. For example, paradigmatic drug innovations like that of propranolol and cimetidine changed the theory of the relevant receptors. In other words, the shaping process of these drugs produced a theory. Science plays a role in the shaping of a drug and *vice versa*. Potent β stimulants caused controversy with regard to their safety and guidelines for their use were set up. Regulations condition the shaping of a drug and *vice versa*. Glaxo earned a huge income from the marketing of ranitidine and became one of the giant pharmaceutical companies in the world. Pharmaceutical companies create drugs and *vice versa*. In addition to them, a lot of actors, factors and activities are produced from the shaping process of a drug: experimental materials, experimental methods, the cognitive ability of researchers, the cognitive ability of the management, knowledge about a new therapeutic area, a new linkage with external specialists, a new strategy, a reputation of the company among doctors, patients and investors, and so on. As I mentioned at the beginning of this chapter, the process of shaping a drug is also a process of co-creating materials, knowledge and institutions.

Thus, the shaping process of drugs is not linear. The linear model of innovation has been mainly criticised for three points. First, there are two-way flows of knowledge between science and technology. (E.g. Faulkner and Senker 1995, pp. 206-211) Second, there are also two-way influences between science and technology on the one hand, and the economy and markets on the other. (E.g. Klein 1985) Third, heterogeneous actors are involved in these interactive relationships. (E.g. McKelvey 1996; Pinch and Bijker 1987) Our findings here, that is to say, the interactive relationship between the four aspects of drug shaping process, are consistent with these three criticisms of the linear model. The shaping process of the drug seems to be better described by the "pinball" model (Webster 1991, p. 47) than by the linear model. Our "pinball" is, however, different from the normal one: first, there are many, various "balls" (elements of drug technology), which are simultaneously bouncing off many, various "pins" (shapers of drug technology); second, the "balls" can combine together and split; third, the "pins" are movable; fourth, some "pins" (human "pins") have their intentions but others not; fifth, there is no strict distinction

between "balls" and "pins"; sixth, there is no external player and it is human "pins" that bring "balls"; seventh, some "pins" may exit and others may enter. It might be more like football with many, sticky balls, which is played in a rain forest! Anyway, the most important point here is that our research demonstrates that this non-linearity and interactivity of the innovation process is applicable even in the pharmaceutical industry, contrary to traditional view held by both practitioners and academics. (See Section 2.1.6). The innovation process is not linear *even* in the pharmaceutical area.

8.2. Types of Pharmaceutical Innovation

When we compare the shaping processes of various drugs described in this study, we can find differences between them. In some cases, the concept of a new drug has no exemplar. Most people inside and outside the organisation are unfamiliar with the concept and wary of it. Therefore, the project leader and co-workers must first persuade people in their company to obtain organisational authorisation. Then if the company decides to develop it, they must persuade outside people such as doctors and regulators. In other cases, the concept of a new drug has an exemplar and few people are suspicious about it. However, there might be another kind of suspicion amongst people in the company: concerning its profitability. Doctors and regulators may fail to find any advantage over the existing drugs of a similar kind. Therefore, the researchers seek to create advantageous characteristics, which are enough to differentiate their drug from others. The company promotes the characteristics amongst doctors and regulators. Thus, the difference in familiarity with the concept of a drug induces distinct patterns as to the shaping of drugs.

We can divide the situation of the shaping of drugs into three types in terms of familiarity: the case in which both the compound and its application are unfamiliar; the case in which the compound is familiar but its application is unfamiliar; and the case in which both of them are familiar.[3] Corresponding with this classification, we

[3] The application in this classification does not mean the therapeutic area itself but the idea of using a compound for the treatment of a specific therapeutic area. For example, in the case of cimetidine, people knew peptic ulcer and wanted an effective drug for it, but no one in advance knew a class of drugs such as cimetidine could be used for the treatment of peptic ulcer.

can identify three types of innovation in the pharmaceutical industry. I name them paradigmatic innovation, application innovation and modification-based innovation, respectively, as in Table 8.1. We examine the characteristics of each of them one by one.

Table 8.1: Three Types of Pharmaceutical Innovation

Type of Innovation	Compound	Application	Examples (relevant chapters)
Paradigmatic innovation	Unfamiliar	Unfamiliar	Propranolol (Ch. 3) British Salbutamol (Ch. 4) British Cimetidine (Ch. 5) British Leuprorelin (Ch. 6) Japanese-American Goserelin depot (Ch. 6) British Mevastatin (Ch. 7) Japanese
Application innovation	Familiar	Unfamiliar	BDP (Ch. 4) British Tamsulosin (Ch. 7) Japanese
Modification-based innovation	Familiar	Familiar	Atenolol (Ch. 3) British Nicardipine (Ch. 3) Japanese Salmeterol (Ch. 4) British Fluticasone propionate (Ch. 4) British Procaterol (Ch. 4) Japanese Ranitidine (Ch. 5) British Famotidine (Ch. 5) Japanese Cefotiam (Ch. 7) Japanese

8.2.1. Paradigmatic Innovation

The first type is paradigmatic innovation, in which neither the compound nor the application is familiar before being shaped. Because the concept of the drug does not have an exemplar but itself constitutes one, we name the innovation that involves such a drug paradigmatic innovation. This is, of course, the analogy of Kuhn's terminology. (Kuhn 1970) Propranolol, salbutamol, cimetidine, leuprorelin, the depot preparation of goserelin and mevastatin can be classified into this type. Following their appearance, drugs with similar molecular structure and the same mode of action

were developed. Several characteristics of paradigmatic innovation can be extracted from the case studies of these drugs.

First, the level of uncertainty is very high. All kinds of uncertainty are involved: scientific, technological, business and regulatory uncertainties. In the case of burimamide, metiamide and cimetidine, the existence of H_2 receptors and their effects on gastric acid secretion was unknown when the search for the compound was conducted. The assay system to identify such a compound was not fully established, either. It was also unclear whether the practitioners would accept such a drug in place of the surgical treatment. In the case of pronethalol and propranolol, the receptor theory was not widely believed when they were looking for drugs based on it. In the case of mevastatin, the existence of HMG-CoA reductase inhibitor was uncertain. The safety of mevastatin was also uncertain. In the cases of leuprorelin and goserelin, their paradoxical effect was unknown. It was also uncertain whether doctors and regulators would accept these drugs.

Second, because of very high uncertainty, the level of doubt about the drug is also very high among people both inside and outside of the company. To shape organisational authorisation, the project leader must persuade the management and other relevant staff in the company. Strong, dauntless leadership is necessary. Endo, for example, did not give up when he faced negative responses from inside the company. He found a way out of adverse circumstances by himself or with help from outside the company. Black did not make a compromise with the idea of developing a drug which was not the H_2-antagonist he had been looking for. His track record and reputation contributed to keep the project alive. Such organisational resistance to innovation and the need of strong leadership seem to be conformable to Donald Schon's argument on the product champion (Schon 1963). However, leaders in drug innovation are probably more properly named project champions than product champions because they have to be active before any product is invented. In addition to the leadership, the clear profiles of the drug are important. In particular, the basic properties of the drug, namely clear efficacy and acceptable safety are essential.

Third, the project leaders and co-workers must do heterogeneous engineering (Law 1987, pp.113-116) to connect up heterogeneous actors, factors and activities in order to achieve the shaping of the compound, the application and organisational authorisation. Endo and his co-workers devised an assay system by themselves, procured animals for experiments, established the linkage with top world scientists in the field and arranged the preliminary clinical trials. The shaping of the market also requires heterogeneous engineering, which is often conducted organisationally. For example, to shape a market for goserelin, ICI's workers developed its depot preparation, supported its clinical trials, demonstrated its advantages over the surgical treatment or other kinds of drugs, explained its mode of action, showed that the "flare-up" phenomenon was not serious, established its production process, obtained approvals for marketing from regulators of various countries, set up its marketing and distributing organisations in these countries and informed doctors about how to use its unique preparation. To achieve this, they had to link a huge number of heterogeneous actors, factors and activities with each other. Thus, the process of paradigmatic innovation can be regarded as the shaping of a new network for innovation.[4]

Fourth, paradigmatic innovation transforms major factors including science, therapy and business. The discovery of pronethalol and propranolol destroyed the then dominant "sympathin" theory and established the receptor theory as a paradigm. The discovery of salbutamol demonstrated the subtypes of adrenergic β receptors. The discovery of burimamide, metiamide and cimetidine also evidenced the existence of H_2 receptors. LHRH analogues led to the discovery of the paradoxical effect and contributed to the relevant research. Mevastatin also played a role in providing evidence of the theory of cholesterol regulation in the body, which had been advanced by Joseph Goldstein and Michael Brown. Thus, paradigmatic innovation transforms scientific theories. It also changes therapies. Cimetidine transformed the main stream of the treatment for peptic ulcer from surgery to internal medicine. LHRH analogues also created a new alternative for the treatment of prostate cancer.

[4] I think that the concept of network here is essentially the same as actor-network (See Section 2.1.3) and that of Galambos and Sewell (1995). At least, the similarity among them is more important for us than the differences.

Mevastatin made the high level of cholesterol in the blood a therapeutic area that could be treated by drugs. This transformation in science and therapy in turn changes business in the pharmaceutical industry in terms of the research strategy, the approaches and targets of research projects, the organisation and approaches of marketing and the conditions of competition.

8.2.2. Application Innovation

The second type is application innovation, in which the profile of the compound is familiar but its application is not. Because it is the application of the drug that is innovative, we name this type application innovation. BDP as inhaled steroid for the treatment of bronchial asthma and tamsulosin for the treatment of urination disorder are examples. These drugs are or can be used in other areas. BDP is used in the dermatological area. Tamsulosin can be developed as a drug for the treatment of hypertension. However, companies developed new applications for strategic reason. There are several characteristics of application innovation.

First, the level of uncertainty is still high, especially in the shaping of the application, organisational authorisation and the market. On the shaping of the application, in the case of BDP, there were various doubts: about efficacy, fear of causing infection and side effects. On organisational authorisation, in the case of tamsulosin, the management had a suspicion about whether the urination disorder would be regarded as a disease, whether doctors would accept the drug, whether patients would go to urogenital clinics to receive such a treatment, and whether the government would give it a price good enough to be accepted by doctors. On the shaping of the market, it is likely to be the case that doctors and regulators are at first doubtful about the advantage of the new drug. It is mainly because the mode of action is unfamiliar to them in this type of innovation. This was seen in the case of tamsulosin, in which doctors initially asked the difference of the drug from others. The answer the company provided was that it was "α_{1c} selective" and the α_{1c} receptors are concentrated in the prostate.

Second, high uncertainty causes suspicion among people in application innovation, as in paradigmatic innovation. Persuasion of these people is important here, too. It is the role of the project leader to obtain organisational authorisation. Evidence of feasibility, marketability and profitability is necessary. Jack, the leader of the BDP project, conducted animal experiments and demonstrated that BDP would work as an inhaled glucocorticoid. Takenaka, the project leader of tamsulosin, himself actively investigated the medical needs for the drug with the marketing staff and obtained convincing data about the potential size of market. For the successful shaping of the market, it is essential that the clinical trials of the drug demonstrate its high efficacy and acceptable safety in the proposed therapeutic area. In addition to this, the company must actively promote the drug. Takenaka and his colleagues mobilised the α_{1c} receptors, which had been just discovered by using biotechnology, to establish the concept of tamsulosin and promote the drug.

Third, heterogeneous engineering is necessary to shape a new application, organisational authorisation and the market. For example, a broad range of different actors, factors and activities had to be connected with each other to accomplish the shaping of these aspects of tamsulosin: the project leader, doctors, local knowledge in medical practice, linkage with doctors, academic physiologists, concepts for the justification of the new application, corporate biologists, toxicologists, an assay system, experimental animals, academic clinicians, epidemic studies, marketing staff, market estimation, the track record of the project leader, the management, the consultant, the regulatory body, chemical engineers, techniques for the separation of isomers, pharmaceutics experts, development of a new preparation for the reduction of side effects, development of an economical production system, clinical trials, collaborative attitude of clinicians, patients, patient education, the change in social needs, a new technique of molecular biology to identify the generic characteristics of receptor subtypes, promotion activities, and so on. In the application innovation, a network including a new set of clinicians is created.

Fourth, application innovation also significantly transforms relevant factors, especially therapy and market. BDP introduced inhaled steroids into the treatment for

bronchial asthma. Tamsulosin created a new market for the medicinal treatment of the urination disorder accompanying benign prostatic hypertrophy. They also changed the business of the companies. With the introduction of BDP, Glaxo obtained full coverage of the treatment for bronchial asthma. The respiratory area became one of the major business areas of Glaxo. Yamanouchi also established its network in the area of urology with tamsulosin.

8.2.3. Modification-based Innovation

If both the profiles of the compound and its application are familiar to relevant people, the innovation of the drug is classified into the third type. We name it modification-based innovation, because profiles of the drug can be seen as modification of those of an exemplary drug. Its examples include atenolol, nicardipine, procaterol, salmeterol, fluticasone propionate, ranitidine, famotidine and cefotiam. However, modification-based innovation is not the same as the incremental innovation, which is often discussed in literature on innovation. The incremental innovation is characterised by bit-by-bit, cumulative improvement, particularly in components of the technological system. This does not include major change in organisational competences and often assumes that its purpose is in efficiency and cost reduction. (Abernathy and Utterback 1978; Tushman and Anderson 1986; Henderson and Clark 1990) Modification-based innovation is not a bit-by-bit kind of innovation. It takes about ten years to develop even a modified drug. It is normally chosen from hundreds of similar compounds, which are secured by patents. In this situation, bit-by-bit improvement is unlikely to happen. It is also difficult to identify components of the product in the pharmaceutical industry as is seen in assembled products. There may not be a need for major change in skills, abilities and knowledge in the organisation when the company already has experience in developing the same kind of drug, as in the case of atenolol, but it is not the case when the company first develops a modified drug, the exemplar of which was developed by another company. The cases of nicardipine, procaterol, ranitidine, famotidine and cefotiam illustrated the latter situation. Therefore, it also seems to be difficult to apply the distinction between competence-destroying discontinuities and

competence-enhancing discontinuities with its original meaning (Tushman and Anderson 1986) to the pharmaceutical innovation. Finally, modification-based pharmaceutical innovation pursues neither efficient production nor cost reduction. Rather, it is fundamentally product innovation. It may cause radical change in the production process. Thus, modification-based innovation is not the same as the incremental innovation. It is perhaps closer to the original notion of normal science (Kuhn 1970) than the incremental innovation. Modification-based innovation is based on past scientific achievement and existing therapeutic approaches and does not challenge them. However, this does not mean either that modification-based innovation is not an organisational challenge, or that it is devoid of radical process change.

Modification-based innovation has several characteristics. First, the level of uncertainty is generally lower than in paradigmatic innovation or application innovation especially in terms of feasibility. However, business uncertainty still remains. Existing patents have to be circumvented. In addition, the condition of competition and the valuation by the regulator are uncertain. Therefore, suspicion about the patentability, marketability and profitability of the drug may arise. In the case of cefotiam, there was a doubt within the company that it was too late to enter the area. Whether the company can develop a drug having a distinct advantage over existing drugs is essential for successful marketing and regulatory application. In other words, the construction of differences is crucial in modification-based innovation. Secondary properties such as selectivity, duration of action and convenient forms of dosage are important, in addition to sufficient efficacy and safety. The cases of atenolol, procaterol and ranitidine well demonstrate this characteristic.

Second, because the main uncertainty springs from business conditions, the decision of the management plays a key role. The strategic, top-down approach is often adopted in modification-based innovation. In this approach, systematic and intensive mobilisation of resources in the organisation is carried out. Clinical trials, production process development, the development of preparations, and the establishment of the

marketing and distributing system are often conducted simultaneously. This is because the speed of development is crucial: rival companies also see the same business opportunity. The keys to the accomplishment of fast development are organisational capability and organisational integration. The case of ranitidine and that of cefotiam well illustrate such an organisational effort.

Third, heterogeneous engineering of the construction of differences is an important activity in modification-based innovation. As we discussed above, the company often conducts a considerable part of this activity in a systematic and organisational way. In this effort, various kinds of factors including new concepts such as "cardio-selectivity," "longer-acting" and "the third generation β stimulants," close relationship with leading clinicians, more convenient forms, a richer variety of forms, papers on comparative clinical trials, instruments and techniques of measurement and analysis to demonstrate the differences between the new drug and existing ones, catch phrases like "Fast, Simple, Safe," users' needs and cost performance are mobilised, as was seen in the cases classified in this type of innovation. For this, relevant actors and their activities have to be linked with each other. If the company has the experience in the development of a drug in the same area, for the most part the network used for this heterogeneous engineering is probably an existing one. How much the company can exploit the network for the shaping of the drug is the main question in modification-based innovation. But if the company does not have the experience, the construction of quite a new network will be required.

Fourth, influences of modification-based innovation on relevant factors are in general more limited than with other types of innovation. Modification-based innovation does not challenge existing paradigms of science and therapy. Rather, it maintains them. However, it may transform market structure and conditions to a great extent. The drugs produced by modification-based innovations often supersede existing drugs including the paradigmatic original, as was demonstrated in the cases of ranitidine and famotidine. Thus, modification-based innovation may provide the company with more money than paradigmatic innovation. This income changes the organisation and the strategy of the company. It also provides resources for further

research and development. Therefore, modification-based innovation may transform not only the market but also the company.

In sum, we can distinguish three types of pharmaceutical innovation classified in terms of familiarity with the concept of a drug, namely paradigmatic innovation, application innovation and modification-based innovation. This implies that the pattern of the shaping of a drug is neither the same nor thoroughly different. This means that the shaping process of a drug is manageable and that the way of its management is not "the one best way." It should be noted that any type is not in particular linked with market success. Ranitidine seemed to be more successful on the market than cimetidine, though it was a modification-based innovation. But this is not the case for every modification-based innovation. In the next section, we will examine the differences between Japanese cases and British cases in terms of the types of innovation.

8.3. Distinctive Features of Japanese Pharmaceutical Innovation

When we look at Table 8.1 from the viewpoint of Japanese – British comparison, we find that most cases of Japanese pharmaceutical innovation belong to modification-based innovation rather than paradigmatic innovation whereas its British counterparts are distributed in a better-balanced way. This is not due to my choice of cases. Other researchers also indicate the same point with using a larger amount of samples. (Hawkins and Reich 1992) On the contrary, I chose mevastatin because it is a rare paradigmatic innovation in Japan. Leuprorelin may also be an exception. However, leuprorelin is probably better regarded as a half-Japanese and half American innovation, because it is unlikely that the drug would have been shaped successfully without the contribution of workers at Abbott and TAP Pharmaceuticals in the United States. Mevastatin was not completed as an innovation because it was discarded halfway through the development. Thus, there is no case in our study that can be seen as an unconditional example of paradigmatic innovation shaped in Japan. This is consistent with the view that is generally held about Japanese pharmaceutical innovation. (Kneller 1999, p. 422; Odagiri and Goto 1996, p. 246; Reich 1990, 134)

It is probable that some historical, structural and cultural factors are related to the tendency of Japanese pharmaceutical industries towards modification-based innovation. In this section, we discuss the factors that are probably related to this tendency, in order to deepen our understanding of the shaping process of a drug. The case studies of the two "almost" paradigmatic innovations involving Japanese companies, namely leuprorelin and mevastatin, are particularly useful to identify such factors.

8.3.1. Level of Science and Technology

As a latecomer amongst industrial countries, Japan has a history of importing scientific knowledge and technology from Western countries. (Odagiri and Goto 1996) Although Japan has made some unique contributions to the progress of science and technology in the pharmaceutical area, it seems that the Japanese level of science and technology in the area was considerably lower than its British and American counterparts at least until the 1970s, the period when most of the drugs examined in this study were discovered. Many Japanese industrial researchers in this study, including Fujino and Matsuzawa in the case of leuprorelin and Endo in the case of mevastatin, studied in the United States. Their experience there led them to the research resulting in the discovery and development of the drugs. All other concepts of the drugs in this study, namely β blockers, Ca antagonists, β_2 stimulants, H_2 antagonists and cephalosporin antibiotics came from British, German or American scientists. Although α_{1c} antagonists seemed to be first named by Yamanouchi's researchers, it was overseas scientists who discovered α_{1c} receptors. These examples indicate that the level of the scientific basis in the pharmaceutical area in Japan was in general lower than such countries as the UK, the US and Germany. This was the case not only in the academia but also in the industry. It was only after 1960 that most large Japanese pharmaceutical companies began to establish their full-scale research laboratories to discover new drugs. (Nihon Yakushi Gakkai 1995, p. 123) Scientific knowledge and technology was not sufficiently accumulated within pharmaceutical companies in the 1970s. They had to send their researchers to foreign and domestic universities to obtain necessary knowledge and skills. An example of

technology transfer from domestic universities to pharmaceutical companies can be seen in the case of nicardipine, in which the techniques for experiments were transferred. Thus, the insufficient level of science and technology in the pharmaceutical area in Japan may be one of the factors explaining the lack of paradigmatic innovation in the country.

8.3.2. Collectiveness of the Organisation

Consensus, interdependence, group-based, overlapping, intensive communication and the sharing of information and knowledge are the concepts that are often used to characterise the Japanese corporate organisation. (Porter, Takeuchi and Sakakibara 2000, pp. 69-76; Fruin 1992, pp. 301-320; Nonaka and Takeuchi 1995, pp.75-83, pp.198-199; Clark and Fujimoto 1991, pp.215-228) These characteristics can be expressed with one word: collectiveness. Collectiveness of the organisation probably contributes to the integration of resources in the organisation but may enhance the level of organisational resistance to unfamiliar ideas and uncertain plans. In the case of mevastatin, Endo, the project leader, faced strong organisational resistance, which almost killed the project, again and again. Unfamiliarity with the concept of the HMG-CoA reductase inhibitor, uncertainty as to its efficacy and safety and the lack of an exemplary drug of the same kind seemed to amplify the doubt among people in the company. The pharmacologists who conducted the tests with rats and the toxicologists who found the unknown crystals in rat cells tried to turn the project down, rather than trying to find an explanation or solution to let it continue. It was Endo's tenacious attitude and the power of academic clinicians that saved the project. The lack of an exemplar also caused doubts within the company in the case of leuprorelin, and became one of the reasons for the delay of its development in Japan. Organisational resistance was observed in other cases of the pharmaceutical innovation in Japan, including nicardipine, tamsulosin and cefotiam. In the case of tamsulosin, the track record of Takenaka, the project leader, contributed to the shaping of organisational authorisation. In other cases, a powerful member of the management backed the project so that it could survive. Thus, the collectiveness of

the Japanese organisation may be another factor that hinders the shaping of the paradigmatic innovation and application innovation in particular.

8.3.3. Exclusiveness of the Market

It is said that the pharmaceutical industry in Japan was nurtured and promoted through a highly regulated market with government-set prices and that health policy served as implicit industrial policy. (Reich 1990, 125) The National Health Insurance, fully established by 1961, promoted the expansion of the Japanese pharmaceutical market in the 1970s. (Reich 1990, 130) The Japanese government has allowed doctors not only to prescribe drugs but also to dispense them. In the obligatory health insurance system, doctors are paid through the fee-for-service reimbursement that is based on the fee schedule lists set by the government. The prescriptions dispensed by doctors are reimbursed to doctors' clinics or hospitals. The margin between the purchase price and the reimbursement price set by the government, called "*yakka saeki*" which is estimated to amount to a quarter of the total sum paid by insurance for pharmaceuticals, has constituted an important source of income and profits to doctors' clinics and hospitals. Therefore, Japanese doctors have had a strong tendency to prescribe drugs in excess of what is needed. (Reich 1990, 130-132; Low, Nakayama and Yoshioka 1999, pp.175-176; Campbell and Ikegami 1998, p.148; Odagiri and Goto 1996, p.244; Howells and Neary 1995, p.236) This also has contributed to the expansion of the Japanese pharmaceutical market. Nowadays, the Japanese pharmaceutical market is the second largest in the world. (Reich 1990, 124; Kneller 1999, p. 411) This large market has enabled Japanese pharmaceutical companies to rely almost on domestic sales alone. Health policy was more advantageous for domestic companies than foreign companies. For example, clinical trials for drug approval had to be conducted in Japan on native people. (Reich 1990, 129) General industrial policies also contributed to the growth of Japanese pharmaceutical companies. Japan restricted investment by foreign companies until the mid 1970s. Until then, the Japanese pharmaceutical market was secured for domestic pharmaceutical companies. (Reich 1990, 133) Patent policy in Japan before 1976 protected only the process technology of drugs, that is to say, if you changed

the method of the production process, you could obtain a patent even if the product was the same. (Reich 1990, 134; Howells and Neary 1995; pp.145-149) Thus, the mixture of industrial policy and health policy in Japan has contributed to the growth of the Japanese pharmaceutical market and the almost exclusive exploitation of the market by domestic companies.

The close relationship between doctors and pharmaceutical companies has also limited the access of foreign companies to the Japanese pharmaceutical market. (Odagiri and Goto 1996, 246; Low, Nakayama and Yoshioka 1999, p.176) Pharmaceutical companies in Japan regard their relationship with doctors as particularly important because doctors have almost decisive power in the choice of drugs and because doctors have substantial power over the national health policy. However, doctors were more powerful in the 1960s and 1970s than at present, and pharmaceutical companies at the time regarded them as if they were "kings." (Low, Nakayama and Yoshioka 1999, pp.175-176, pp.178-180; Reich 1990, 132; Campbell and Ikegami 1998, pp.27-29, pp.31-32, pp.129-131; Howell and Neary 1995, pp.28-29, pp.54-55) This power relationship between doctors and companies explains why Endo was able to reverse the trend of opinion within the company by mobilising a doctor's offer of a clinical trial of mevastatin. To establish a good relationship with such a powerful actor, pharmaceutical companies in Japan have made a lot of effort by deploying a large number of representatives. (Odagiri and Goto 1996, 246) This has functioned as an entry barrier for foreign companies.

It is said that the relationship between the government and pharmaceutical companies has been more ambivalent. The pharmaceutical industry is not a major political power-base in Japan. (Howells and Neary 1995, p.55) The pharmaceutical industry is not under the jurisdiction of the Ministry of International Trade and Industry (MITI) but under the Ministry of Health and Welfare (MHW). The former has characteristics as a promoter of industry, but the latter is essentially a regulatory body even though it has some promoting functions as well. (Howells and Neary 1995, p. 191, pp.239-240, p.251) Thus, on the one hand, the MHW looks powerful and has seemingly had no hesitation in imposing drug price cuts and other policies on the

industry. (Howells and Neary 1995, p. 237, p.249) On the other hand, however, the close links between the MHW and pharmaceutical companies are often mentioned. (Howells and Neary 1995, p.139) As was revealed in the scandal of Green Cross, one of the large pharmaceutical companies in Japan, many retired senior bureaucrats of the MHW seem to have joined the pharmaceutical industry. (Low, Nakayama and Yoshioka 1999, pp. 176-177; Reich 1990, 137) Pharmaceutical companies have provided senior bureaucrats with longer job opportunities. These ex-bureaucrats probably play an important role as mediators between the industry and the MHW. Thus, formally, the relationship between the government and pharmaceutical companies in Japan appears to be of an arm-length kind, but informally it may be closer.

The mixture of health and industrial policies, the relationship between doctors and pharmaceutical companies, and the relationship between the MHW and the companies have constructed a large, closed market in Japan. This closed market has provided Japanese pharmaceutical companies with opportunity for earning satisfactory profits. However, at the same time, it may have prevented the companies from paying attention to overseas markets[5]. (Reich 1990, 128) This may in turn have reduced the incentives to discover and develop internationally competitive drugs with unique concepts and higher uncertainty. Instead, modification-based innovation is probably preferable as long as it is marketable and profitable in the domestic market. That is to say, the closed and protected market in Japan limited the vision of domestic pharmaceutical companies to less uncertain opportunities to earn profits. In other words, the bounded vision (Fransman 1990, p.3, p.286) of pharmaceutical companies is directed to modification-based innovation by structural factors including health policy, industrial policy, the relationship between doctors and companies, and that between the regulator and companies.

Several other institutional factors also seemed to promote modification-based innovation in Japan. Pharmaceutical price policy was one of them. Since 1981, the

[5] This constitutes a clear contrast with British pharmaceutical companies, which had to face international competition early on because the UK market was not secured for them but open for foreign companies. (Owen 1999, p.371; Owen 1994)

MHW has reduced the reimbursement price of drugs. (Campbell and Ikegami 1998, p.158) This has had an unintended impact on innovation-seeking activity in the pharmaceutical industry. Doctors responded to the price cuts by shifting their prescription patterns to products with higher profit margins, that is, new drugs. This stimulated pharmaceutical companies to introduce new drugs frequently. However, these new drugs did not have to be truly innovative drugs. (Reich 1990, 137) It is only since 1989 that the MHW has distinguished between innovative drugs called "*picashin*" and less innovative drugs called "*zoroshin*" and has promoted the former. (Howells and Neary 1995, p.126) Until then, the approval policy and price policy had unintentionally promoted modification-based innovation rather than paradigmatic innovation.

In sum, these factors, namely the level of relevant science and technology, the collectiveness of the Japanese organisation and the exclusiveness of the Japanese pharmaceutical market, probably contributed to the Japanese companies' tendency towards modification-based innovation. However, because these factors themselves have been historically and socially shaped, they will not last forever. This means some paradigmatic innovations may emerge from Japan. But it cannot be shaped by the effort of pharmaceutical companies alone. Many relevant factors mentioned above also have to be changed. And this will need enormous effort by many people in Japan.

8.4. Concluding Remarks

8.4.1. The Shaping Process of Drugs Is Not Linear

The conclusion of this study is that the pharmaceutical innovation process is not linear. The linear model of technological change is not applicable even to the pharmaceutical industry, contrary to the common views of both practitioners and academics. Drug innovations happen neither from science, via technology, to market, nor from social needs, via science and technology, to market. The process of pharmaceutical innovation is interactive and multilateral. Numerous actors, entities

and their relationships are involved in the process. Even within a pharmaceutical company, there are many actors whose views and interests are different. Drugs are shaped by interaction among various actors, factors and activities. The four aspects of the shaping process of drugs, namely the shaping of the compound, of the application, of organisational authorisation and of the market, are interactive, inter-reflective and co-evolving. The compound, its application, its organisational authorisation and its market are shaped together and together constitute a drug. They are also interdependent: if one of them is dissolved, then the rest will also become unstable and dissolved. The shaping process of drugs also transforms relevant actors, factors and activities, including science, technology, artefacts, organisations, human relationships, organisational relationships and market. The shaping of drugs is, therefore, the co-creation of materials, knowledge and institutions. Thus, three major points of the criticism of the linear model – the interaction between science and technology, the interaction between science/technology and economy/market, and the involvement of heterogeneous actors in the interactions – are indeed applicable to pharmaceutical innovation. The linear model has lost its last bastion!

This non-linearity of drug shaping process has several practical implications. In order to promote innovation in the pharmaceutical industry, financial and material support in research must help but is not sufficient. The shaping of drugs consists not only of research but also of development, in-house politics and market creation. For example, creating opportunities for communication between drug researchers and clinicians in various therapeutic areas in terms of drug development, between the management of pharmaceutical companies and external scientific and medical experts and patients in terms of drug assessment, and between companies, regulators, doctors, academics, patients and general public in terms of drug marketing are all ways which would probably be effective in stimulating innovation. An integrative approach, which includes all aspects of drug shaping and pays attention to not only economic but also "social"[6] means of promotion, is necessary. Without intervening in the "social" side of the shaping process of drugs, innovation-promoting campaigns in the pharmaceutical industry will be less efficient and less effective.

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[6] With regard to the term "social" here, see Section 2.3.4.

Although innovation process is not linear, either in the pharmaceutical industry or in other industries, there are several differences. For example, with regard to the comparison with other industries, such as automobiles and electronics which are sometimes characterised by incremental innovations, the innovation process in pharmaceuticals seems to be more strongly linked with science and with regulation. External sources of scientific knowledge more directly take part in the shaping process of technology. This is consistent with the argument of Faulkner and Senker (1995, pp.208-209), which compared knowledge flows from universities into companies in three "high-tech" areas, biotechnology, engineering ceramics and parallel computing. Regulation is often paid little attention in the innovation model (e.g. Klein 1985), but it is an essential factor in any aspect of drug shaping. Thus, these are two distinctive features of the innovation model in pharmaceuticals compared with other industries.

8.4.2. Both Human Actors and Non-human Entities Are Essential

It should be noted that non-human entities play an indispensable, but not decisive, role in the shaping process of drugs. This research basically supports the key claim of actor-network theory that technology is a heterogeneous network. (See Section 2.1.3) Neither people alone nor things alone can shape drugs. Although this sounds obvious, it should be emphasized because it reminds us of the material imperative, that is to say, the fact that non-humans strongly restrict all our activities, though their restriction is not deterministic. This suggests, for example, that the distribution of physical resources (e.g. scientific apparatus, or disease-model animals) in an economy affects the shaping of drugs. It also implies that the material infrastructure, including stable energy, good materials, excellent production equipment and efficient logistic means, also influences the performance of drug innovation. In particular, it was seen in our case studies that the level of such industries as scientific instruments and production equipment is essential for the shaping of not only compounds but also their organisational status (in terms of acceptable production costs) and market (as

regards demonstrating their efficacy and safety). It should be also noted that the shaping process of drugs itself produces new material imperatives.

8.4.3. There Are Different Types of Drug Innovation

The shaping processes of different drugs are neither the same nor completely different. We found three distinguishable patterns in terms of the relative level of uncertainty of each aspect. In paradigmatic innovation, uncertainty is high in all aspects. In application innovation, uncertainty is high in all aspects except the compound. In modification-based innovation, uncertainty is high in the shaping of organisation authorisation and that of the market. These three types of drug innovation have different characteristics in the shaping process. Paradigmatic innovation is characterised by strong resistance within the organisation and suspicion outside the organisation. Therefore, it needs strong leadership to accomplish innovation. Leaders also have to combine heterogeneous factors inside and outside the organisation to construct all aspects of the drug. In application innovation, linkage with clinicians in the new application area is particularly important in order to identify new applications of known compounds. Strong leadership can be also required to overcome considerable resistance inside and outside the company against the unfamiliar use of a familiar compound. The construction of a new network in the new therapeutic area is also needed. In the modification-based area, though uncertainty in the creation of the compound and its application is not so high, there is uncertainty in patentability, marketability and profitability of the new drug. Therefore, the creation of differences is the key task. It also requires swift development, because the opportunity cost due to delay is clearer. An organisational capability to conduct systematic and intensive development is needed. There are also differences in the degree of impact of innovation on relevant actors, entities and factors among the different types of innovation. The impact of innovation is most significant in paradigmatic innovation and least significant in modification-based innovation.

With regard to the relationship between the types of innovation and the four aspects shaping drugs, in paradigmatic innovation, all aspects of the drug shaping are important: in the shaping of the compound and its application, the fusion of external and internal knowledge is particularly significant; in the shaping of organisational authorisation and the market, persuading people about the efficacy and safety is the key task. In application innovation, the shaping of application is obviously essential. Linkage with external knowledge, in particular communication with clinicians in various areas is important. In terms of the shaping of organisational authorisation and the market, it is necessary to persuade people of the efficacy of the new application. In modification-based innovation, in the shaping of the compound, avoiding the patents of other companies is one major problem. Constructing differences from existing drugs is another. In the shaping of organisational authorisation, persuading the management of its marketability and profitability is critical. In the shaping of the market, persuading customers and regulators of the differences of the drug is necessary. Thus, different kinds of innovation have differences in the order of emphasis on the four aspects of shaping drugs and require different activities in each aspect.

It seems difficult, and perhaps unwise in terms of risk "portfolio," for a drug company to pursue exclusively any one of the types of drug innovation, given that there is keen competition between companies in the same therapeutic areas and that it takes about ten years to develop a drug. In addition, although the three types of innovation possess differences in drug shaping process, they also have similarities, for example, relevant actors, entities and activities and their interactive relationships. Therefore, the management of drug innovation for each innovation seems not to be completely mutually exclusive. Nevertheless, there seems to be different points of emphasis in the management of different types of drug innovation. To promote paradigmatic innovation, the reduction of organisational and regulatory resistance is needed. However, this resistance is necessary to protect the company and society from the undesirable results that might come from the development of inappropriate drugs. Proper assessment of projects is required. For this, it seems effective to encourage communication between various external scientific and medical experts,

and the management and the regulator. The management and the regulator should be also aware of the constructed nature of scientific knowledge. Even though dominant scientific knowledge is inconsistent with the concept of a new drug, it can be possible that existing scientific knowledge has flaws. To promote application innovation, the communication between corporate researchers and clinicians in various therapeutic areas seems important. The communications between researchers in different areas and between researchers and marketing staff in various therapeutic areas also seem to be helpful. In order to promote modification-based innovation, building the integrated organisation is crucial so that the development of drug can be swiftly achieved. Communication with medical practitioners and patients may be helpful to identify the needs for improvement.

In sum, the shaping processes of drugs are neither identical nor radically different. There are three types of innovation, namely, paradigmatic innovation, application innovation and modification-based innovation. Each innovation has different characteristics in the shaping process of drugs, and so the shaping process of drugs should be managed somewhat differently, according to the type of innovation.

8.4.4. Drug Innovation in Japan: Historical, Cultural and Structural Factors

As discussed in Section 8.3, when we compare the Japanese cases with the British cases, the proportion of modification-based innovation seems to be higher in Japan than in the UK. Historical, cultural and structural factors, namely the relatively lower level of science and technology in the biomedical area in Japan, the "collectiveness" of Japanese organisations and the exclusiveness of the Japanese pharmaceutical market seem to contribute to this orientation of Japanese companies toward modification-based innovation. That is to say, these features of the Japanese context in which drug innovations take place seem to be more favourable for modification-based innovation than for paradigmatic innovation. These contextual features of Japanese pharmaceutical innovation are not always shared with other industries in Japan. The levels of science and technology vary between different fields of R&D. The structure and the openness of market also seem to vary between different

industries. However, the collectiveness of organisations seems to be common in Japan, although its effects on innovation may be different between industries. In the industries in which their scientific base is relatively stable, market needs are better articulated and incremental innovations are dominant. In these industries, such as the automobile industry and the electronics industry, consensus-based, collective organisation is probably favourable for innovation. However, in the pharmaceutical industry, such organisation may be inappropriate to particular types of innovation, namely, paradigmatic innovation and application innovation because unfamiliar ideas cannot be easily accepted by all relevant actors in the organisation.

Thus, the comparison between Japanese and British pharmaceutical innovation shows that historically, culturally and structurally formed factors, for example, the level of science and technology, properties of organisations, and properties of markets, affect the pattern of drug shaping process. It supports the arguments of the social shaping of technology that historical and structural context should not be ignored in understanding technological change. (See Section 2.1.4) These influences from contextual factors are less obvious than influences from directly involved actors such as researchers, managements, doctors and regulators. This implies that in order to understand the process of technological change we should take into account not only observable actors, factors and activities in each individual innovation process, but also hidden factors characterising the context in which innovations take place. In terms of research methods, comparative studies of innovation between different historical, structural and cultural contexts are necessary to understand innovation process fully.

From the practical point of view, the involvement of historical, cultural and structural factors in drug innovation process suggests that broader transformations of society may be required in order to change the pattern of innovation. For example, to promote paradigmatic innovation in Japan, it may be necessary to transform its scientific and technological culture, organisational culture and market structure. Relevant scientific and technological jobs in Japan should be made more attractive for young people and foreign people with ability. The research infrastructure should

be improved, and flows of knowledge between public sector researches and industries should be promoted. Heterogeneity and heterodoxy in organisation should be allowed. Unfamiliar things should be tried rather than being avoided. The market should be open wide to foreign companies and the competition among them should be encouraged so that Japanese companies can have larger incentive to paradigmatic innovation. It is obvious that these transformations require more than the effort of pharmaceutical companies alone. Scientists, engineers, educators, managers, investors, doctors, regulators, policy planners, citizens, patients, their carers and family members should each play their role. In other words, everybody is, indeed, to some extent involved in the shaping process of a drug. If we want better medicines, we should be aware of this, think about our roles and play the roles.

8.4.5. Reflexive Remarks

As the final remarks of the thesis, I would like to note several things. I have learnt about the research process in the course of this study. First, I have learnt that there is a kind of "snow-ball effect" in acquiring access to interviewees. That is to say, if I can obtain an agreement about interviewing from a person or company of great repute, it becomes easier for me to get another agreement. There are two routes for obtaining contacts: the personal route from one person to another and the formal route from companies' spokespersons through their management to their researchers and staff. In taking either route, I mentioned my track record in interviews when I asked for another interview, which seemed to help me acquire an agreement. In the company-route case, spokespersons also seemed interested in which companies were included in my list of interviewees. Interestingly, it seemed to me that building the list of interviewees by the personal-route was more difficult in Japan than in the United Kingdom. In Japan, the formal, company-route seemed easier. This might suggest the cultural properties of both countries: more individualistic British society and more institutional (corporative) Japanese society. Second, despite the snow-ball effect, I could not achieve access to the full range of researchers and staff related to each case. Companies did not always allow me to meet people who I wanted to interview with. This can cause the exclusion of diverse views of the drug shaping

process. I tried to minimise the potential biases due to this exclusion by using written evidence by different authors. In fact, I am afraid that not all interviewees feel happy about my story, which are different from theirs because of different evidence. When I showed my early draft of each case to relevant interviewees, some of them expressed specific disagreements with my account. Therefore, my story is not the same as the interviewee's story. Since my methodology ran the risk of generating a "great man" view of innovation, it is to some degree reassuring that at least some "great men" were unhappy with my account. However, my thesis does rely greatly upon interviews of key researchers and there still remains room for a richer account due to the fact. Thirdly, it was found that follow-up communication with interviewees was very important to acquire additional information to understand the case processes of shaping drugs. In the course of reconstruction of cases, it was usual for me to come across questions which had not come to mind in the interview. Therefore, I have learnt that it is important to ask interviewees to allow follow-up communication after interviewing. Fourthly, there was a potential tension between the author and interviewees and relevant companies over the contents of the story of drug shaping. As mentioned above, some interviewees and companies seemed uncomfortable with my account. However, fortunately, all interviewees were generous enough to tolerate my different views. It should be noticed, however, that there is a risk of the rejection of cooperation by interviewees and companies if the interviewer fails to obtain their trust. Therefore, I have learnt that it is essential for the interviewer to be sincere and careful enough to obtain the trust of interviewees. Fifthly, I have learnt that it is extremely difficult to obtain internal documents on drug discovery and development, such as the notebooks and letters of researchers and the minutes of company meetings. In some cases, I did ask interviewees for such documents, but they declined my request because of the reason of confidentiality. I have to admit that this limitation of my feasible data collection restricted the kind of analysis that I could do. For example, it was difficult to conduct a full analysis in terms of the sociology of scientific knowledge with the available data. However, I also confirmed that scientific papers are useful sources of information about the shaping of drugs. Although we should be careful about the non-constructivist style of these papers, they sometimes show controversies, as was seen in Chapter 4. Given the extremely

difficult situation in obtaining internal documents about drug R&D, contents of specialist scientific papers should be examined carefully in order to find traces of "social" aspects of drug shaping. Knowing these things about the research process especially in the area of the pharmaceutical industry, I would be able to build up evidence more efficiently with less trials and errors.

The other remarks are about questions that remain. First, how general are the findings of this study? Are the four aspects of drug shaping and the three types of drug innovation applicable to other drug innovations? Are they applicable to newer drug innovations, which are based on biotechnology? Are the types of innovation size-dependent? When taking the division of labour, for example, between large pharmaceutical companies and small and medium sized biotech companies into consideration, how do the models of innovation change? I conjecture that modification-based innovation may be size-dependent in the sense of being easier in large companies because the uncertainty in R&D is relatively low and integrated and speedy mobilisation of resources for drug development is crucial to success. In contrast, I conjecture that paradigmatic innovation and application innovation may be less size-dependent. Small companies may have a smaller stake in existing ways of doing things and therefore are likely to be more favourable to unfamiliar ideas; but they may be counterbalanced by the fact that they are likely to have less resources necessary to develop a new drug. To answer these questions, case studies of newer drug innovations, especially of biotechnology-based ones, and quantitative studies based on the framework of this study would be useful. Second, how deep does the process of social construction go in the shaping of medicines? To reveal this, more internal and detailed evidence, more informants and the fuller use of the sociology of scientific knowledge will help. Third, how are inter-organisational linkages related to the shaping process of drugs? For example, how do knowledge transfers between rivals, between universities and industries and between small biotech firms and large pharmaceutical companies take place? How do these different organisations conflict and collaborate with each other? How do these relationships contribute to drug innovation? Studies of inter-organisational linkages in the drug innovation process will be meaningful. Fourth, how applicable are the findings here to innovations in

other industries? To answer this, comparative studies between different industries based on our framework will be needed. To explore the shaping processes of drug and other technologies fully, we should use different perspectives, different research methods, and different data.

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